The association between Attention Bias Modification and basal cortisol in individuals with vulnerability for reoccurring depression

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Abstract

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Background and research aim: Depression constitutes a great burden in the world population, with its high reoccurrence rates. One of the factors in both the maintenance and reoccurrence in depression is a negative attention bias, which leads to an increase in stress appraisal. The current study aimed to investigate the association between modifying a negative attention bias and basal circadian cortisol variations in previously depressed individuals.

Methods: The data in the current study was collected from the project "Secondary prevention of depression applying an experimental Attention Bias Modification procedure", where the author has worked and been part of the data collecting process. 52 participants who had a history of depression but who were currently in remission were recruited, and received either an active or placebo version of a computerized Attention Bias Modification (ABM) task, over 14-days consisting of 28 sessions in total. The participants' basal circadian cortisol variations were measured using three saliva samples for each time of measurement, pre-intervention, after 14 days and at one-month follow up. A mixed between-within analysis of variance was used in the analyses of the data.

Results: Even though there were no statistically significant differences between the basal circadian cortisol variations at either time of measurement between the two groups, there were tendencies in the predicted direction with a reduction in basal cortisol in the active ABM group. A general learning effect of the ABM task, entailing a decrease in reaction times were found in both groups although the ABM task did not appear to have a specific effect on positive vigilance. There was however fluctuations in the attention biases in both groups, and these fluctuations appeared to be smaller in the active ABM group.

Conclusion: Attention biases in remission phases of depression might reflect more dynamic processes instead of stable traits, influenced by mood. Reducing fluctuations in these biases through the ABM task might reduce residual symptoms like a heightened level of basal cortisol. The current null-findings could have been affected by different factors:

number of previous depressive episodes, remission criteria, comorbid anxiety disorders, establishing reliable basal circadian cortisol measures, and sample size. The findings of the current study is considered to be a small but important contribution to the field of attention bias modification and depression, in terms of re-evaluating different aspects of the intervention.

Acknowledgments

Being a part of the research project “Secondary prevention of depression applying an experimental Attention Bias Modification procedure” over the past two years have been a great opportunity to learn more about the field of depression and new, targeted treatments.

I am grateful for all the counseling and help I have received from my supervisor Nils Inge Landrø, and my co-supervisors Rune Jonassen and Catherine Harmer, who have been very patient and supportive during this process. It has been an extremely learning full experience, working on the project, investigating the data for the current study and writing this thesis.

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1 Introduction

1.1 Background – depression, a "leading cause of world disability"

Depression stems from the Latin word deprimere, which means; "to press down, depress" (Oxford Dictionaries Online, n.d.). As a construct today, depression is used to describe what is considered to be the clinical form of a lowered mood, or being pressed down, with its key characteristics. The World Health Organization (WHO) defines depression as "a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration" (Marcus, Yasamy, Van Ommeren, Chisholm, & Saxena, 2012). This definition entails both the psychological, physiological and the executive features of depression. The different components affect and reinforce each other at various levels. The psychological themes evolve around a negative evaluation of one self, rejection from others, loneliness, helplessness and a loss of meaning (Beck, 2008). These themes affect and are affected by important components in depression which are cognitive biases in attention, perception and memory. Both the psychological and executive components appear to influence the stress response system. Dysregulation in the stress response system with a heightened level of basal cortisol is one of the physiological features in depression, that is also frequently seen also in remission periods (Huber, Issa, Schik, & Wolf, 2006).

Depression is a huge burden for both the people suffering from it, and for the society as a whole, when accounting for years lost due to disability. According to WHO (Marcus et al., 2012) depression is the most highly occurring psychiatric disorder in the world, with a lifetime prevalence of 17%. Further WHO estimates that "by 2020, depression will be the second leading cause of world disability" (Marcus et al., 2012), "and by 2030 the largest contributor to disease burden" (Marcus et al., 2012).

Depression has an estimated reoccurrence rate of about 80% (Browning, Holmes, Charles, Cowen, & Harmer, 2012). It is difficult to find the most effective targeted psychotherapy and psychopharmacology treatments to prevent reoccurrence in depression. Antidepressants appear not to have the desired effects on many people suffering from depression, and different forms of psychotherapy have variable degrees of success rates (Cuijpers, Smit, Bohlmeijer, Hollon, & Andersson, 2010; Kirsch et al., 2008). An increased knowledge of the phenomenon depression, its underlying and maintaining factors, and how to target these, are therefore necessary and important. New forms of treatments that target

maintaining factors in order to prevent reoccurring episodes can make important contributions in the attempt to reduce the burden of the disorder.

1.2 Negative attention bias

Cognitive biases with regards to both detecting negative information through attention, and memory biases for negative events have been proposed as maintaining factors in depression (Mathews & MacLeod, 2005). Both people suffering from depression and those in remission appears to have a heightened memory for recalling negative events (Mathews & MacLeod, 2005). In order to perceive a situation as negative one has to detect and attend to negative stimuli. A negative attention bias has been established as an underlying mechanism for reoccurrence in depression, and has been proposed to increase the degree of reactivity to stress (Browning et al., 2012; De Raedt & Koster, 2010; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Koster, Fox, & MacLeod, 2009; Mathews & MacLeod, 2005). A bias can be defined as "a tendency to process information so as to favor types of emotional valence or meaning" (Mathews & MacLeod, 2005). According to Beck (2008) a bias towards negative stimuli stems from cognitive schemas. Cognitive schemas are defined by Beck as "a cognitive structure for screening, coding, and evaluating the stimuli that impinge on the organism" (Beck, 1967). In other words, a schema is a way of organizing information into categories (e.g different experiences). Taken into account the extreme number of stimuli a person is exposed to every day, we are dependent on efficient information processing in order to adapt to and cope with our surroundings. Categorizing allows information processes to be automated, making us capable to process several stimuli at a time and adapt quickly.

However, schemas can also be dysfunctional and maladaptive, which is often seen in depression. Certain experiences can have a greater impact on the organization of for example self-schemas, which are "accessible information about the self" (Hammen, Marks, DeMayo, & Mayol, 1985). Early adverse events like the loss of a parent in childhood, can lead to dysfunctional attitudes about one self, like "If I loose a loved one I am helpless"(Beck, 2008) or "I am alone in the world". These attitudes can become unified into self-schemas that contains central themes in depression like hopelessness and loneliness that can lead to loss of motivation and suicidal wishes. Such schemas can be viewed as a cognitive vulnerability for depression (Beck, 2008). Similar experiences at a later point in time that evoke associations to the early negative event(s), can activate the depressive self-schemas. The cognitive schemas can be viewed as the center of a complex network, encompassing behavioral, affective, motivational and physiological components. When this network is fully activated, it

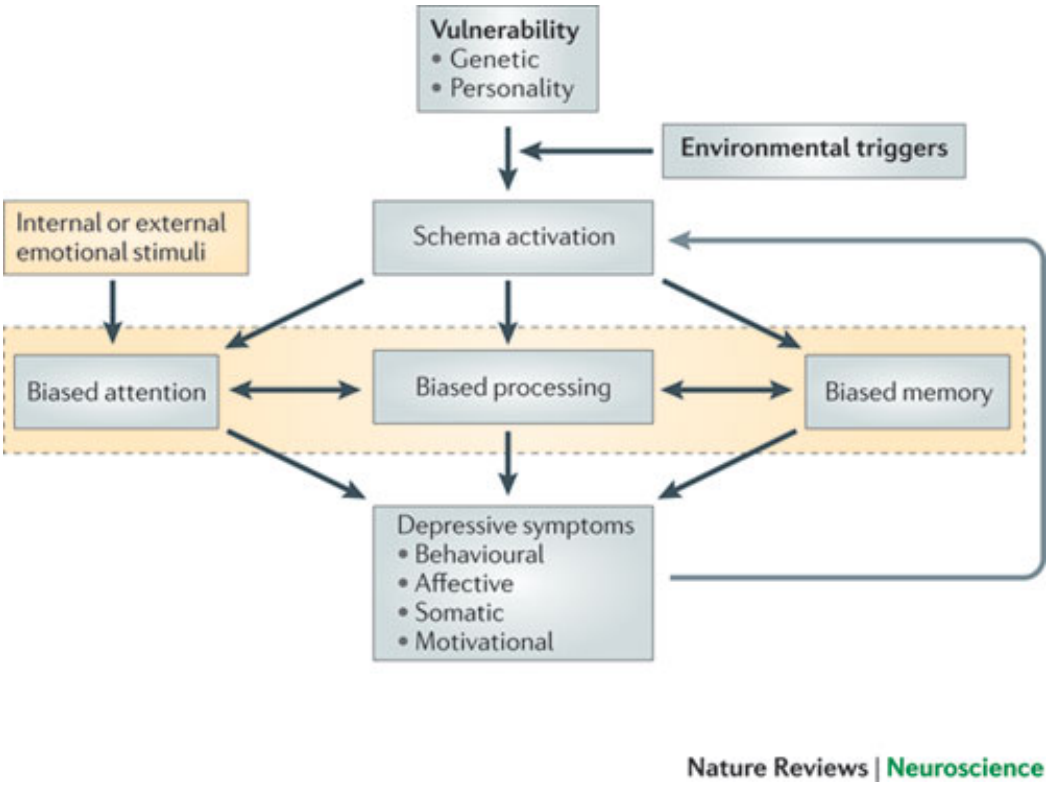
represents the numerous symptoms of depression, and becomes resistant to external influence like positive stimuli. The resources from adaptive schemas are disproportionally distributed to the dysfunctional schema(s), reducing a person's ability for coping and problem solving (Beck, 2008). Thus resulting in a negative bias in information processing, which can be argued to be the core mechanism in the maintenance and recurrence in depression (Beck, 2008). See Figure 1. Repeated activation of the dysfunctional cognitive schemas leads to a "kindling effect" (Beck, 2008) which means that with time they become more readily activated, and more resistant to change. As with neurons, when the network is activated, the connections between the different components are strengthened "cells that fire together, wire together"(Schatz, 1992). Consistent with the fact that for each depressive episode the probability for recurring episodes increases (Browning et al., 2012; Liu & Alloy, 2010).

According to Beck (1967), individuals suffering or recovering from depression, will only show a negative attention bias towards stimuli that are compatible with their depressive schemas. This bias appears to be most prominent with regards to stimuli of interpersonal significance, like facial expressions (Gotlib et al., 2004; Liu & Alloy, 2010). Such stimuli can activate depressive schemas, which lead to a suppression of more positive, adaptive schemas. A negative attention bias entails that already at the encoding level, the attention is drawn to possible, negative stimuli. The decoding part of a detected negative stimulus will be done during activation of a depressive schema, leading to a negative evaluation of the situation. Such situations will be perceived as stressful, activating the stress response system. A negative attention bias therefore leads to a more frequent generation of stress at an information processing level through the detection of negative stimuli.

In individuals who are in remission from depression, these schemas or networks are latent but not activated. However, depressive self-schemas appear to change with mood (Beck, 2008; Hammen et al., 1985). A negative attention bias can be viewed as a more stable trait when the depressive schemas are fully activated during a depressive episode. In remission, these biases might be more fluctuating in accordance with mood induced activation of these schemas. In a study by Zvielli, Amir, Goldstein, and Bernstein (2015) it is suggested that attention biases might be better understood and regarded as dynamic processes instead of static traits. Zvielli et al. (2015) proposes that it is the underlying biased emotional attention towards content specific stimuli (i.e. threatening stimuli in anxiety disorders, and negative facial expression in depression), which fluctuate and has to be addressed in order to modify the attention biases.

The current study will not focus on genetic vulnerabilities in depression, but it is still worth mentioning that not all individuals that experiences early adverse life events develop depression. There appears to be individual predisposing vulnerabilities with regards to genetic variations affecting both attention and the stress response system, which interacts with stressful experiences leading to the development of depression, and making these individuals more prone to the development of depressive self-schemas, as described (Beck, 2008).

Figure 1. Becks model of information processing in the cognitive model of depression



Note. The illustration of the model is retrieved from the article by Disner, Beevers, Haigh, and Beck (2011) in Nature Reviews.

1.3 The stress response system and cortisol

Stress and coping are two closely related concepts. The definition of stress can be understood in terms of an organism's capacity or incapacity to cope with a stressful stimulus. When the demands of a situation or certain circumstances exceeds an organism's perceived resources, or ability to cope, it can be defined as stressful (McEwen, 1998). Stress can be further defined as either acute or chronic. Acute stress is a short-term stress response to a stressful stimulus that can elicit adaptive responses in terms of the fight or flight response,

which consists of rapid changes in neurotransmitters and hormones enabling us to quickly respond in a threatening situation. The stress response system is an adaptive or allostatic system, that adapts to stimuli in order to maintain and regain homeostasis or equality in the body's internal environment." Allostasis is the ability to achieve stability through change" (McEwen, 1998). When the stress response system for some reason is unable to adapt to changes, it leads to a physiological stress reaction that can be referred to as chronic stress or allostatic load (McEwen, 1998). Acute and chronic stress has different effects on the central nervous system.

1.3.1 The short- and long-term effects of stress on the central nervous system

There are two main systems involved in stress responses. Even though these are connected, they play different roles in the immediate and the more prolonged responses to stress. The sympathetic-adrenomedullary (SAM) system is involved in the fight or flight response through the instant release of mainly epinephrine (adrenalin) from the central adrenal glands, preparing the muscles to fight or flee (Gunnar & Quevedo, 2007). The hypothalamic-pituitary-adrenocortical (HPA) system initiates the slower and more prolonged responses to stressors, through the release of glucorticoids (GCs), which in humans are mainly cortisol. The effects of cortisol are more gradual as opposed to the instant effects of adrenalin. The pathway of cortisol release starts in the paraventricular nuclei (PVN) of the hypothalamus, were both corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) are released. CRH and AVP affect the anterior pituitary's release of adrenocorticotropic hormone (ACTH), which travels to the adrenal glands attaching to receptors, which elicits the release of cortisol (Gunnar & Quevedo, 2007). Cortisol, unlike adrenaline, crosses the blood-brain barrier to a much higher degree, affecting the central nervous system to a greater extent. Levels of cortisol can be affected by a number of different factors like age, gender, seasonal changes, circadian rhythm, medications and psychological disorders (Kirschbaum & Hellhammer, 1994; Pariante, Thomas, Lovestone, Makoff, & Kerwin, 2004; Van Cauter, Leproult, & Kupfer, 1996; Wehr, 1998).

1.3.2 The stress response system in depressed and previously depressed individuals - the damaging effects of long duration exposure to high cortisol levels

People suffering from depression seem to have a dysregulated stress response system. There is an increased reactivity of the amygdala, which may escalate the frequency of stress appraisal (Beck, 2008). This leads to an increase in cortisol release throughout circadian

rhythms, 24-hours variations, which can result in hypercortisolism, an excessive release of cortisol at both resting states and in response to stressful situations (Holsboer, 2001). These prolonged elevated cortisol levels, makes it hard for the stress response system to react and activate the needed amount of extra resources when faced with stressors (Harkness, Stewart, & Wynne-Edwards, 2011).

Cortisol interacts with two different receptors; glucorticoid receptors (GR) and mineralocorticoid receptors (MR). MR keeps the everyday functions of the systems operative, while GR make us adapt in more stressful situations, where we need to access more resources than what is required in initial functioning. Cortisol has a higher binding affinity to MR, and only when cortisol exceeds initial levels during stressful situations, does cortisol bind to GR. Cortisol has important and beneficial functions in the central nervous system. With initial to moderate levels of cortisol acting through MR and GR, neural plasticity is enhanced by reducing the refractory period of neurons in the hippocampus. This means that the neurons reach their action potential more quickly, so that they are ready to fire and communicate with other neurons (de Kloet, Oitzl, & Joëls, 1999). However, when cortisol exceeds moderate levels, and a much higher percentage of GR receptors are occupied, this can lead to a reduction in glucose availability which over time can led to cell death. One of the brain areas which has a high density of cortisol receptors is the hippocampus and associated areas (McEwen, 1998). The hippocampus functions as a negative feedback site for the HPA system to regain homeostasis. High cortisol exposure over time, can lead to the loss of important receptors in this region for a functional regulation of the HPA axis. This can be caused by a down regulation of the number of receptors in order to regain homeostasis, and to possible destruction of these receptors as a result of high cortisol levels that become toxic. The results can be hypercortisolism, frequently seen in depression (Holsboer, 2001). Some studies have shown a higher risk for relapse associated with reduced negative feedback ability, in previously depressed individuals currently in remission (Zobel et al., 2001). This indicates that some individuals have a continued dysregulation of the HPA axis even in remission, which appears to be a risk factor for recurring depressive episodes. Somatic consequences of hypercortisolism over time can lead to secondary illnesses like osteoporosis, atherosclerosis, metabolic syndromes and reduced immune system capacity. Left untreated, these diseases contribute to a reduction in life expectancy by 15-20 years (Tsigos & Chrousos, 2002)

Other structures in the limbic system such as the amygdala in addition to prefrontal structures, also modulates and controls the HPA system (Gunnar & Quevedo, 2007). The amygdala is crucial for emotional interpretation and consolidation of emotional events. It also

plays an important role in activating the HPA system to psychosocial stressors. Frequent and high levels of stress can lead to a sensitization of the amygdala, which entails easily evoked responses to stressors, due to a lowered threshold for action potentials in neurons, making activation easy (Gunnar & Quevedo, 2007). In resemblance to cognitive schemas, this represents a kindling effect. In depressed and previously depressed individuals, the capacity of top-down control of limbic structures from prefrontal areas seems to be reduced, while limbic activation, especially in the amygdala, appears to be increased, or hyper responsive (Beck, 2008).

The stress response system and its ability to efficiently up and down regulate itself when faced with stressors (McEwen, 1998), is dependent on the initial value of basal cortisol levels (Lacey, 1956). Basal cortisol, or baseline levels, refers to an individuals normal level of cortisol concentrations when the system is not faced with stressors. If the overall basal cortisol levels are high, this can result in a reduced reactivity, meaning that the stress response system has a decreased ability to react adaptively to stress, with regards to both up and down regulation, due to initial high basal cortisol. Basal cortisol variations follows a curve according to circadian rhythms, variations over 24 hours, where cortisol levels are highest in the early morning hours, and then gradually decline in the evening, reaching a low point around midnight (Wehr, 1998). In both depressed and previously depressed individuals, this curve of cortisol between evening to morning seems to be flatten (Sjögren, Leanderson, & Kristenson, 2006), due to high basal cortisol concentrations.

The current study looks at basal circadian cortisol variations from evening to morning, which can be used as an assessment of HPA axis functioning. By assessing the variations from evening to morning, at three different times over a one-month period, where possible changes in cortisol levels will be compared. This gives a more comprehensive view of the tonic instead of just the phasic variations in cortisol. Phasic changes entail more rapid changes during a short time-interval, like the cortisol awakening response (CAR), where cortisol samples are taken during one consecutive hour after awakening. Especially a blunted CAR in depressed and previously depressed patients has been a consistent finding (Huber et al., 2006). The tonic changes that emerge over time, ranging from daily variations to weeks and months, are less investigated.

The effect of cortisol on executive functioning, including attention, has been widely studied (Andreotti, Garrard, Venkatraman, & Compas, 2014). Cognitive functioning during a depressive episode have been shown to be negatively affected (Preiss et al., 2009). It appears that even when in remission, previously depressed individuals score significantly lower than

never depressed controls on both the Trail Making test, part B and on the STROOP color-word task. These tests both measures executive functioning, and respectively degree of cognitive flexibility with regards to alternate-switch abilities, and degree of inhibition control (Meiran, Diamond, Toder, & Nemets, 2011; Preiss et al., 2009). In addition, number of previous depressive episodes have been indicated to affect the degree of cognitive impairment in remission (Biringer et al., 2005).

There appears to be a relationship between cognitive components and cortisol. Whether this relationship is one-directional or bi-directional is however less investigated. There is limited research on whether modifying cognitive components can affect cortisol.

1.4 The relationship between a negative attention bias and cortisol

Modifying a negative attention bias can be argued to lead to a reduction in stress appraisal, which would affect one of the residual symptoms of depression; high basal cortisol levels with subsequent reduced cortisol reactivity.

Assessing a stimuli as stressful happens when the individual perceives the stimuli or situation as over exceeding his or hers resources, or ability to cope. With a bias towards negative, content specific stimuli (e.g. sad faces and a sense of rejection) previously depressed individuals are vulnerable to negative mood changes. This has been hypothesized to activate depressive schemas, resulting in an appraisal of a reduced ability to cope. In turn, in an attempt to deal with the stressors, this leads to activation of the HPA axis in order to regain homeostasis. However, with a hyper responsive HPA axis, and possible reduced negative feedback ability, the body keeps releasing cortisol, resulting in high basal cortisol concentrations. In addition, the activation of depressive schemas will maintain a negative attention bias, which will continue the stressful assessment of the individual's surroundings. In sum the negative attention bias and cortisol release becomes a feedback loop that reinforce each other, making people who have experienced one or more depressive episode, vulnerable for reoccurring episodes.

The amygdala plays a crucial role in both stress responses and in evaluation of emotional stimuli. In previously depressed individuals there appears to be a hyper-responsive amygdala activation (Browning, Holmes, & Harmer, 2010). Modifying a negative attention bias that entails an over-representation of negative detected stimuli, could lead to a reduction in amygdala specific activation. A reduced hyper responsive amygdala, could affect the HPA axis in the direction of a possibly more adaptive stress response system with reduced basal cortisol concentrations, leading to a more efficient ability to up and down regulate itself when

faced with stressors. Changing a negative attention bias can therefore be argued to lead to a reduction in stress appraisal, which would affect one of the residual symptoms of depression; high basal circadian cortisol with subsequent reduced cortisol reactivity.

One of the advantages with intervening at an attention level when people have recovered from a depressive episode is their increased ability to respond to external stimuli. As mentioned, a depressive episode can be viewed as a full-blown activation of the depressive network with its cognitive, physiological, behavioral and emotional components. When fully activated the network allows for little external influence to correct the dysfunctional attitudes that are present.

1.5 The Attention Bias Modification (ABM) procedure

Cognitive Bias Modification (CBM) have been a field of research aiming to target and modifying biases with regards to attention, interpretation and memory (MacLeod, Koster, & Fox, 2009). Through computerized procedures with different content and duration, although still in its early stages, this research has shown some promising results with regards to transference to clinical applications (Browning et al., 2010; Koster & Bernstein, 2015). One of the most commonly used CBM techniques developed to target attention biases in depression is the Attention Bias Modification (ABM) procedure (Koster & Bernstein, 2015). Findings of a negative attention bias in depressed and previously depressed individuals, has been especially consistent when the stimuli presented has been mood congruent faces, instead of words. Processing of pictures and faces depends on a different system than processing of words. Faces and pictures seems to have an easier access to the system where emotional information is stored (Gotlib et al., 2004). Building on the principle that previously depressed individuals have a content specific attention bias especially with regards to stimuli of interpersonal significance (e.g. faces) that can activate depressive schemas, the ABM uses faces that are of different emotional valence.

Studies using CBM procedures has shown promising results especially in patients suffering from anxiety disorders (MacLeod et al., 2009). In a study using an ABM procedure with people diagnosed with generalized social anxiety disorder (GAD), 72% of the participants in the active condition did not meet the criteria for GAD one month after the intervention compared to 11% in the control group (Schmidt, Richey, Buckner, & Timpano, 2009). This effect gives an indication about ABM procedures being translational to clinical settings, and might also be possible to produce in samples of clinical depressed and previously depressed individuals. There is a high comorbidity between anxiety disorders and

depression, and these affective disorders have some similar but yet distinctive features (Kaufman & Charney, 2000). For example, biases in anxiety disorders and depression might occur at different stages of the attention process. The attention bias in anxiety disorders appears to be an extremely quick, subconscious process, occurring from 10-500 milliseconds (ms). Whereas in depression, the attention bias seems to entail the later stages of attention occurring from 500-1000ms, with an additional problem of disengaging attention away from negative stimuli (Browning et al., 2010; Gotlib et al., 2004).

Having a more positive attention bias appears to "protect against the negative effects of stressful environmental interactions" (Browning et al., 2012), which increases previously depressed individuals coping skills when faced with stressors. In the study by Browning et al. (2012) previously depressed individuals showed a decrease in morning cortisol concentrations following an active version of the ABM task. The sample size was however smaller than in the current study, and cortisol was only measured in the morning as opposed to investigating circadian cortisol variations as in the current study.

The computerized active ABM task trains participants to attend to more positive faces, through a dot-probe paradigm. Participants are presented with pairs of facial expressions for a certain amount of ms, which are followed by one or two dot(s) behind the most positive weighted of the two faces. Valid trials are when the dot(s) appears after the most positive valence faces, while invalid trials are when the dot(s) appears behind the most negative valence face. In the active condition of the task, there are mostly valid trials. Participants then have to indicate with one of two keys on the keyboard, whether one or two dot(s) appeared. The underlying assumption is that through associative learning, which is a well-established phenomenon (Fanselow & Poulos, 2005), between positive facial expressions and the dot-probe, participants gradually develop an attention towards more positively facial expressions over the training period that will be consolidated and generalized to their everyday life. This attention towards more positive weighted stimuli is thought to be a protection against stress, through both the reduced detection of negative stimuli and actions based on these negative evaluations. The effects of different CBM tasks, have been shown to last for up until 4 months when an increased amount of sessions are administrated over several weeks (MacLeod et al., 2009). As opposed to CBM tasks done at one single point in time, which has yielded effects lasting for only 20 minutes to 24 hours (Fox, Mackintosh, & Holmes, 2014). Consolidating an improved bias towards more positive valance facial expressions over time could be argued to increase the possibility of a more robust change in bias that would protect against stress vulnerability.

1.6 Summarized

A negative attention bias is one of the maintaining factors in depression, which can be viewed as the center of depressive schemas. These schemas encompass emotional, cognitive and physiological components, one of which is a dysregulated stress response with an excessive cortisol release. In remission phases these schemas can be activated by negative mood changes. The negative attention bias and the excessive cortisol release becomes a feedback loop that reinforce each other, making people who have experienced one or more depressive episode, vulnerable for reoccurring episodes.

The active version of the ABM task have been shown to have a positive effect on cortisol levels through its influence on attentions bias that have been proposed to work as a cognitive vaccine against residual symptoms including cortisol (Browning et al., 2012). Correction of a negative attention bias can therefore be said to reduce risk factors for recurring depressive episodes.

1.7 Research hypotheses in the current study

The current study has one primary outcome measures, basal circadian cortisol, which aims to explore the association between ABM and stress. The primary outcome measure is validated and used in three main research hypotheses:

1. Measures of basal cortisol in previously depressed individuals will reveal a circadian pattern characterized by a drop in the evening and an increase in the morning from the first to the second morning sample.
2. The active ABM condition will modify basal circadian cortisol levels. It is predicted that 14-days of ABM training would be associated with lower basal circadian cortisol levels.
3. The effect of ABM will be more noticeable after one-month follow-up than directly after the training procedure.

The first hypothesis is that cortisol concentrations will increase from the first to the second morning sample, and decrease in the evening, in both of the groups at all three times of measurement. This is the expected circadian curve of normal basal cortisol. In previously depressed patients this curve can be somewhat blunted, but is still expected to have the same decrease in the evening, and increase in the morning. It is important to establish whether or

not these expected cortisol levels can be observed in both of the groups, before comparing possible differences due to the intervention.

The second hypothesis is that there will be a difference in basal circadian cortisol variations between the two groups after the 14-days intervention. The third hypothesis is that this effect will be more apparent at one-month follow up than after 14-days. If affecting a negative attention bias can have an impact on morning cortisol levels as shown in the study by Browning et al. (2012) with a smaller sample, this effect should also be apparent in basal circadian cortisol variations, encompassing the changes from evening to morning. Some studies have found a maintained but also increased effect of cognitive bias modification task several months after the intervention (Schmidt et al., 2009). These increased effects might reflect an ongoing process and gradually consolidation of cognitive changes (MacLeod et al., 2009). This might partly reflect changes in amygdala hyper responsiveness through a modification of a negative attention bias that would be gradual, with a reduced kindling effect of amygdala activation. Such possible effects would therefore be more apparent after a certain amount of time. The predicted differences in the cortisol curves are decreased basal cortisol concentrations in the evening and morning in the active ABM condition group, compared to the placebo ABM condition group. This reflects both phasic cortisol, defined as changes within cortisol curves over one consecutive day from evening to morning, and tonic changes that emerges over time, which is defined as the comparison of the three different cortisol curves over a one month period.

The secondary aims involve the ABM task itself. Establishing a general learning effect of the ABM task, meaning that both groups regardless of condition will show a general learning effect of the task, entailing a decrease in reaction time towards both valid and invalid trials over the 14 days intervention. This is an important assumption to establish at a group level, in order to ensure that the participants have completed their ABM sessions, which is a necessary prerequisite in order to compare possible differences between the placebo and active conditions. In addition, the ABM procedure is further explored by calculating the mean intra-individual learning effects and differences between valid and invalid trials, to investigate possible fluctuation in biases. These secondary aims may shed light over some of the controversies in CBM research. Studies have yielded results ranging from null-effects to statistically significant effects on clinically relevant outcome measures. These findings have however mostly been from small to moderate (Koster & Bernstein, 2015). Many studies investigating the effects of the ABM procedure, has not properly established the task in terms of establishing a general learning effect showing that participants regardless of conditions

have completed the task in a satisfactory way (i.e. completed session and paying attention during them). In addition, biases have mostly been studied as a stable trait, not as possibly more dynamic processes. This is important to review more closely, in order to validate the phenomenon one is trying to influence. Herein, the current study explores the ABM procedure by calculating the general inter-individual learning effect and differences between valid and invalid trials over the training procedure to look at possible fluctuation in biases.

Secondary aims regarding the ABM task are:

- Establishing a general learning effect of the ABM task.
- Investigating possible fluctuations in biases.

2 Methods and materials

2.1 Context

The current study used data collected in the project ”Secondary prevention of depression applying an experimental Attention Bias Modification procedure”. The main project was started in 2014, and is based at the Department of Psychology at the University of Oslo (UiO). It is currently being conducted at both the University in Oslo and in two clinical centers in Norway. The project is lead by professor Nils Inge Landrø, in collaboration with the University of Oxford. The core aim of the main project is secondary prevention of depression in previously depressed adult patients, by modification of a negative attention bias through the computerized Attention bias modification (ABM) procedure, seen in relation to candidate genes for serotonin transportation/reuptake. The main project is ongoing, and will consist of results from approximately 400-500 participants when completed. The main project received funding from the research council of Norway, through the research programme on mental health in 2013. The main project is approved by the regional ethical committee (REC) 2014/217-1.

The current study uses a sub-sample of the participants from the main project. The participants were recruited from, “Kveldspoliklinikken raskere tilbake” at Vinderen Distriktpsykiatriske senter (DPS), and had completed their one-month follow up between May 2014 and May 2015.

2.2 Participants and recruitment

In cooperation with the outpatient clinic at Vinderen DPS, Diakonhjemmet Hospital in Oslo, 76 participants with a history of one or more previous depressive episodes were recruited. Former patients previously treated for depression, consenting to be contacted from relevant research projects, received an invitation with detailed information about the study. The main aim of the study on the invitation was stated to be “investigating attention focus, how it changes over time and how it is related to mood and depressive symptoms”. The invitation also contained detailed information about what participation would entail and that participation was voluntary. There was also information stating that participation in the study would have no direct benefits or disadvantages to the participants. After the invitation had been received, employees from the study called the previous patients to inquire whether or not they were interested in participating, answering possible questions and giving additional

information when required. Written consents were collected from the participants preceding the diagnostic assessment and evaluation for participation in the project.

Inclusion criteria were a history of one or more previous depressive episodes, in addition to currently being in remission. This entailed meeting the criteria for one or more previous depressive episodes (ICD-10 F.32.0 Mild depressive episode, F32.1 Moderate depressive episode, F32.2 Severe depressive episode without psychotic symptoms or F.33.4 Recurrent depressive disorder, currently in remission(World Health, 1993)). Exclusion criteria`s were no current or past neurological illness, bipolar disorder, psychosis or drug addiction. Diagnostic assessment and evaluation of remission was made in accordance with the structured clinical interviews for DSM-IV criteria, The Mini International Neuropsychiatric Interview (M.I.N.I.), and the Beck Depression Inventory (BDI-II). Employees at the study trained in administrating M.I.N.I., conducted the assessment at the Department of Psychology at UiO.

2.3 The Beck depression inventory II (BDI-II)

The Beck depression inventory (BDI) was developed in 1961 based on clinical observations of depressed patients as a self-report screening tool encompassing the different aspects of clinical depression (Beck, Steer, & Carbin, 1988). There are 21 items with scores ranging from 0-3 on each item, reflecting symptom intensity during the last two weeks (Beck et al., 1988). The inventory takes approximately 5-10 minutes to fill out. The total score is achieved through adding the sum of scores on all the 21 items, giving a range of scores between 0-63. A score of 0-9 indicates a minimal of depressive symptoms, a score of 10-18 indicates mild depression, a score from 19-29 indicates moderate depression and a score from 30-63 indicate severe depression. The second edition, BDI-II is today widely used and accepted as a self-report measure that has a high inter-rater reliability and validity. In addition to discriminating depression from other mood disorders sharing many of the same features such as anxiety disorders (Beck et al., 1988; Dozois, Dobson, & Ahnberg, 1998; Riedel et al., 2010). A BDI-II score of < 12 has been found by some to produce the highest degrees of sensitivity and specificity with regards to remission criteria (Riedel et al., 2010). The current study uses a BDI-II score of < 12 as one of the remission criteria's.

Within the scope of the current study and its focus, BDI-II scores were only obtained preceding the intervention in order to compare self-reported symptom levels.

2.4 The Mini International Neuropsychiatric Interview (M.I.N.I) version 6.0.0

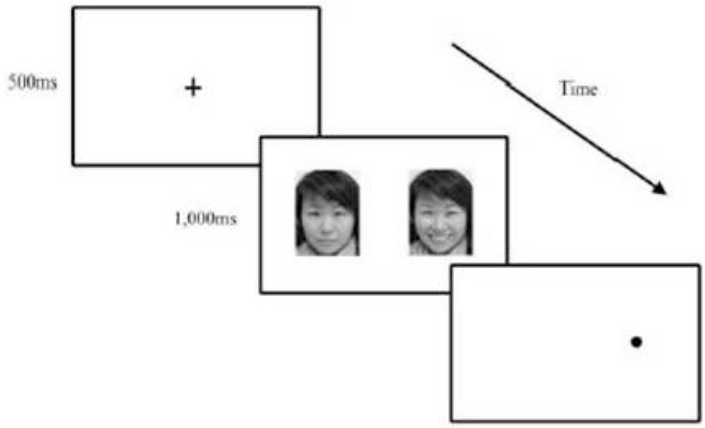
The M.I.N.I. interview is a structured clinical interview, designed for brief assessments of 23 symptom disorders on axis 1 from the DSM, with yes or no answers (Mordal, Gundersen, & Bramness, 2010). When using the MINI interview for diagnostic assessments according to the ICD-10, the diagnostic guidelines in accordance with the ICD-10 must also be met. Mordal et al. (2010) found a high inter-rater reliability (cohens kappa of .82) between interviewers for the Norwegian translated version, when assessing current and recurrent depressive disorder.

2.5 The ABM Task

The current study intervenes at the level of an implicit, systematic negative attention bias in emotional information processing. Attempting to modify this bias in order to attain a more functional attention focus, through a computerized ABM task. The participants are instructed to focus on a cross in the middle of the screen of a laptop, and indicate whether one or two dot(s) appear after a pair of faces is presented on the screen, using two different keys on the keyboard of the laptop. Pairs of facial expressions with different emotional valence, neutral, sad, or happy, appear next to each other and are presented for either 500ms or 1000ms. Following are either one or two closely linked probes in one of the locations of the two faces, and the participant then have to indicate if one or two probes were presented. The reaction time is then measured assessing the amount of ms from when the dot(s) appeared to a key is pressed. Depressed and previously depressed individuals shows a faster reaction time when the probe(s) follows negative valence faces, as opposed to never depressed individuals who on the contrary shows a slower reaction time when the probe(s) follows negative facial expressions (Browning et al., 2012).

There are two conditions in the current study, a placebo condition were there are no weighting towards either negative or positive valence faces, and an active condition. In order to correct the implicit negative attention bias, participants are given an active condition of the ABM procedure, where the probe(s) appears 87% of the time in the location of the most positive valence facial expression in the pairs (neutral-negative, negative-happy, happy-neutral). In order to detect the probes, participants learn at an implicit level that there is an association between the probe(s) and the positive valence facial expressions, directing their attention towards the positive valence faces. This is thought to results in an associative learned attention bias towards positive stimuli.

Figure 2. The ABM task



Note. Depicting a valid trial from an ABM task, where the dot appears behind the most positive valence emotional expression to the right, and the presentation time of the faces are 1000ms.

2.6 Measures of cortisol

Cortisol concentrations in the current study were measured over a one-month period, at three different times: before the ABM intervention, after the 14-days intervention and at one-month follow up. At each different time, three saliva samples were collected, giving a total of nine samples. Before the intervention: (1) in the evening before the starting the 14-days intervention, (2) upon awakening the same morning the participants started the ABM task, (3) 15 minutes after awakening. After the 14-days ABM intervention: (4) the last evening of the intervention, (5) upon awakening the morning after completing the ABM task, (6) 15 minutes after the first morning sample. At one-month follow up: (7) in the evening, (8) upon awakening, (9) 15 minutes after the first morning sample.

The cortisol saliva samples were collected using the Sarstedt Cortisol Salivette® Device, which consists of a tube with a cotton swab, that participants are instructed to chew on in order to attain a viable sample, and then place back into the tube. Participants were given instructions on how to collect these saliva samples at home, including time of sampling, which was in the evening between 20-22, and in the morning between 07-09. The participants were also told to avoid activities entailing exercise, use of tobacco, teeth brushing, eating and drinking 60 minutes before collecting the saliva sample, as they can affect cortisol concentrations and (Kirschbaum & Hellhammer, 1994). The samples were delivered by the participants to the Department of psychology at UiO and stored in a freezer at -18℃, and within 4 months all samples were transferred to -80℃ freezers. The samples are thawed on ice and cold centrifuged at 4℃, 2000 rpm for 15 minutes. The saliva is then transferred into

eppendorf tubes, which are stored in a -80℃ freezer. Samples are brought to Radbound University in Nijmegen on dry ice for radioimmunoassay (RIA) analysis.

The protocol used for cortisol RIA in micro plates is refined by Gorissen et al. (2012). In short 3-5 plates were prepared each day, using 96-wells Micro-Assay-Plates (Greiner-Bio-one: 655094; White/μClear - high-binding). Wells are prepared by adding cortisol antibody *(Abcam: ab1949; Cortisol Antibody[xm210] monoclonal and IgG purified)* diluted in coating buffer into all wells, except A-specifics that received coating buffer only. Plates were incubated overnight at 4℃. Following incubation wells were washed with wash buffer and then block buffer, consecutively plates were placed in heat cabinet at 37℃ for incubation. Saliva samples were thawed on ice for ~1-2 hours. Blocking buffer was removed from the wells by decanting and immediately thereafter standards *(Sigma: H4001-5G; Hydrocortisone ≥98% HPLC)*, samples and controls (assay buffer) were added in duplicate. Finally 90μl ^{3}H-Cortisol tracer *(PerkinElmer: #NET396250UC - Hydrocortisone (Cortisol,[1,2,6,7-^{3}H(N)]-),[1,2,6,7-^{3}H(N)]- 250*μCi(9.25MBq) was added into each well and left to cold incubate over night at 4℃. After incubation plates were repeatedly washed with wash buffer. Prior to β-measurement scintillation solution was added to all the plates. Values that were obtained were directly translated into saliva cortisol concentrations.

2.7 Procedure

Participants were randomized to either the placebo or active ABM condition. It was a double blind study, were both the employees interviewing participants and the participants were blind to which condition they received.

2.8 Statistical analysis and data reduction

All analyses were conducted using IBM SPSS Statistics version 22.0.0.0. To explore possible group differences with regards to age, educational level, BDI-II scores, number of previous depressive episodes, independent t-tests were used. When comparing gender, and comorbid anxiety disorders, chi-squared tests were applied.

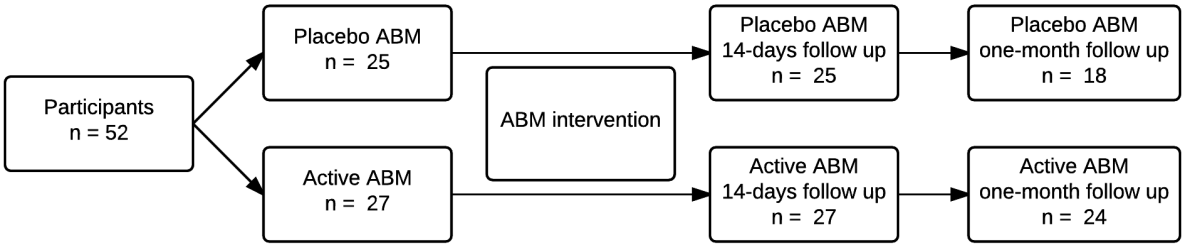
Of the 76 participants some were excludes due to the following reasons: 14 of the participants were diagnosed as being in a current depressive episode. These participants were excluded, since the focus of the current study was attention bias modification in relation to basal circadian cortisol in previously depressed individuals. 8 participants were excluded du

to extreme levels of cortisol excretion more than 3 standard deviations from the group mean. 2 participants were excluded due to more than 4 lost ABM sessions.

In total 52 participants were include. 20 of these participants did also fulfilled the criteria's for different anxiety disorders, including panic disorder, limited panic attacks, and social phobia. Given the high comorbidity between anxiety disorders and depression, it was expected that a relatively high number of the participants would also have a comorbid anxiety disorder (Kaufman & Charney, 2000), and these participants were included.

10 participants lacked all of the three cortisol samples for the one-month follow up. This high number was mostly due to constraints in the cortisol analyses. Data analyses were carried out on all available data for the cortisol samples, which were 52 participants preceding the intervention, 52 after the 14-days intervention, and 42 at the one-month follow up, giving different sample sizes at the different times of measurement. See Figure 3.

Figure 3. Overview of participants in the ABM conditions over the one-month period



Note. Depicting number of participants in the two different conditions with respective sample sizes from randomization, at the 14-days follow up, and at the one-month follow up.

The following model was used to investigate the hypotheses regarding basal circadian cortisol variations in both groups: a mixed between-within analysis of variance was conducted with the two ABM groups (placebo versus active) as the between-subjects factor, and the three samples pre intervention, at 14-days follow up and at one-month follow up, as within-subjects factors. The dependent variable was basal circadian cortisol, defined as the circadian variations from evening to morning.

Table 1.The cortisol samples at the different times of measurement

Pre-intervention (T1)		
E (1)	M1 (2)	M2 (3)
14-days follow up (T2)		
E (4)	M1 (5)	M2 (6)
One month-follow up (T3)		
E (7)	M1 (8)	M2 (9)

Note. Overview of the Evening (E), Morning 1(M1) and Morning 2 (M2) samples at the different times of measurement.

To look at possible changes between the separate cortisol samples, the difference between corresponding samples were calculated (e.g. for comparison of T1 and T2, the difference score between E(4) and E(1), M1(5) and M1(2), and M2 (6) and M2 (3) was calculated). The same was done between all the three different times of measurement, T1, T2 and T3. See Table 1.

The following model was used to investigate the secondary aims, which was that both of the groups would show a general learning effect of the ABM task and that there would be possible fluctuation in biases: a mixed between-within subjects analysis of variance was conducted with the two ABM groups (placebo versus active), as the between-subjects factor, and time over the 14-days intervention period as a within subjects factor. The dependent variable was reaction time.

3 Results

3.1 Group demographics and baseline measures

The two groups were well matched in all the samples both pre intervention, at 14-days follow up and at one-month follow up with regards to the demographic variables age and educational level. The age range was between 27-67 years. The groups were also well matched with regards to clinical variables entailing symptom levels measured by the BDI-II preceding the intervention and comorbid anxiety disorders. There was however a clear trend in differences between the groups when it came to number of previous depressive episodes.

Since there was a variation in the number of participants in the two different conditions pre, at 14-days follow up and after one-month, separate t-tests and chi-squared tests were conducted for the groups pre intervention and at 14-days follow up, and after one month in order to compare possible differences between the two ABM condition groups also with regards to the different sample sizes.

All effects are reported as significant at $p < .05$.

Table 2. Participant demograpics and clinical information

	The sample pre and at 14-days follow up (*n* = 52)		**The sample at one-mont follow up (*n* = 42)**	
	Placebo ABM (*n* = 25)	**Active ABM (*n*=27)**	**Placebo ABM (*n*= 18)**	**Active ABM (*n*=24)**
Age Mean (SD), Years	43.9 (9.4)	41 (9.1)	45.33 (9.6)	41.25 (9.4)
Sex, n, F:M	16:9	17:10	15:4	15:9
Educational level, ISCED (SD),	2.5 (.6)	2.51 (.6)	2.57 (.5)	2.46 (.6)
No. of previous episodes Mean (SD)	3.1 (1.3)	4.0 (2.2)	2.9 (1.2)	3.9 (.5)
BDI-II scores pre, Mean (SD)	9.1 (7.1)	11.9 (6.3)		
Comorbid anxiety disorders , *n*	17	14	13	12

ISCED level, referring to International Standard Classification of Education (Unesco, 1997), was divided into three categories, 1 = upper secondary education, 2 = tertiary education 1-4 years, and 3 = tertiary education for more than 4 years. On average the participants in both groups had an educational level corresponding to tertiary education ranging from 1-4 years.

The placebo groups mean symptom level on the BDI-II equaled a minimal of depressive symptoms, while the group mean symptom level in the active ABM group equaled mild depression. Both of the groups fulfilled the criteria for self-reported measure for remission, which was defined as a score of < 12. The mean level in the active group was 11.9, meaning that this result was just within the criteria score for remission.

In both the samples consisting of 52 and 42 participants, the placebo ABM group had a mean of around 3 previous depressive episodes, while the active ABM group had a mean of around 4 previous depressive episodes. In the sample consisting of 52 participants, there was a clear trend between the placebo ABM group and the active ABM group $t(50) = -1.86$, $p = .07$. In the sample consisting of 42 participants at one-month follow up, there was a clear trend between the placebo ABM group and the active ABM group $t(41) = -1.89$, $p = .07$. Since this difference was at a trend level it was included as a covariate.

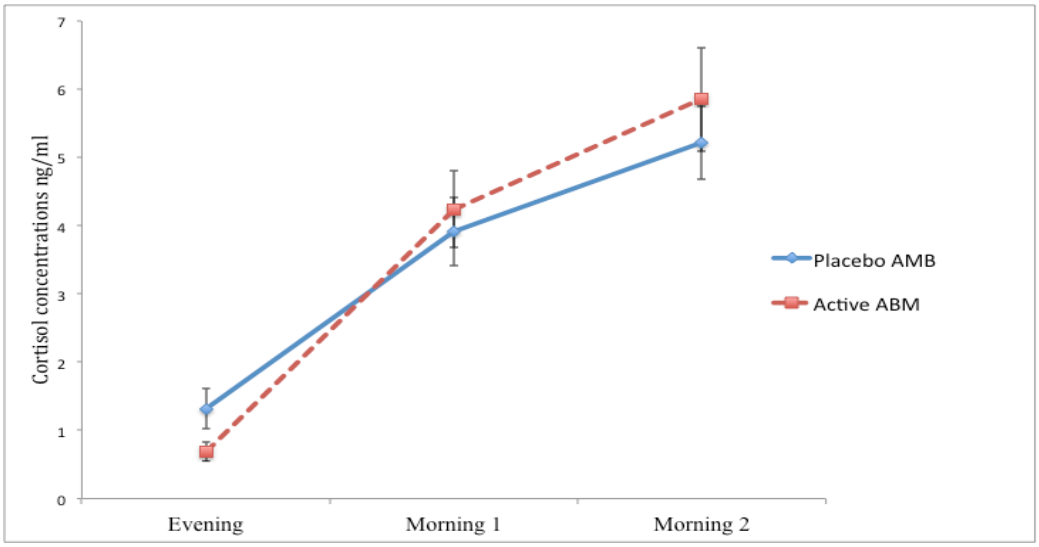
3.2 The curves of basal circadian cortisol from the different times of measurement

The first hypothesis was that basal circadian cortisol variations would decrease in the evening and then increase from the first to the second morning sample, in both of the groups at all three times of measurement. This was a consistent finding at all the three times of measurement, pre intervention, at 14-days follow up and at one-month follow up. Before the intervention, there was a statistical significant main effect of time, Wilks` Lambda = .79, $F(2, 48) = 6.60$, $p = .00$. These results gave the predicted cortisol curve with a decrease in basal cortisol levels in the evening and an increase from the first to the second sample in the morning. See Figure 4. The same pattern was seen after the 14-days intervention, were there was also a statistically significant main effect of time, Wilks` Lambda = .61, $F(2, 48) = 15.44$, $p = .00$. See Figure 5. At one-month follow up, this predicted cortisol curve persisted with a statistically significant main effect of time, Wilks` Lambda = .64, $F(2, 38) = 10.51$, $p = .00$. See Figure 6.

In the basal circadian cortisol curve before the ABM intervention, the evening sample in the placebo ABM group had a mean of 1.32 with a standard error (SE) of 0.30, and in the active ABM group a mean of 0.69 and a SE of 0.14. The Morning 1 sample in the placebo

ABM group had a mean of 3.91 with a SE of 0.50, and the active ABM group had a mean of 4.24 and a SE of 0.56. The Morning 2 sample in the placebo ABM group had a mean of 5.22 and a SE of 0.54, and in the active ABM group with a mean of 5.85 and a SE of 0.76. See Figure 4.

Figure 4. Basal circadian cortisol variations before the ABM intervention



Note. Depicting basal circadian cortisol variations from evening to morning before the ABM intervention. Cortisol concentrations measured in nanogram(ng)per/milliliter(ml) in the evening (Evening), upon wakening (Morning 1) and 15 minutes after the first morning sample (Morning 2). The filled line shows the placebo ABM group, and the dotted line shows the active ABM group.

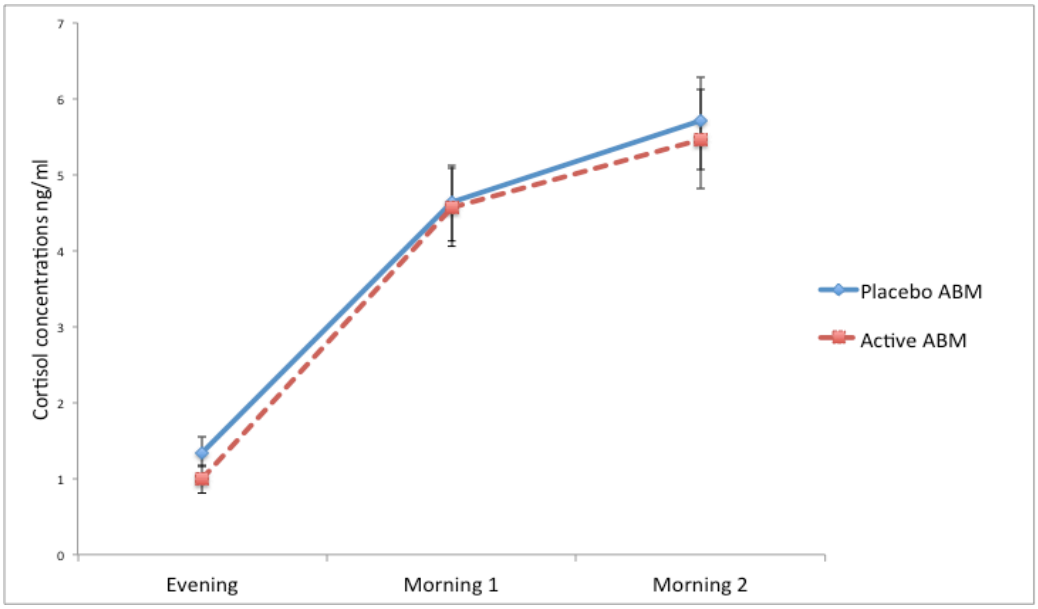
3.3 Analyses of variance for the relationship between the ABM intervention and basal circadian cortisol levels

The second hypothesis was that there would be a difference in basal circadian cortisol variations between the two groups after the 14-days intervention period. There was no statistically significant interaction effect between the ABM conditions and basal circadian cortisol after the 14-days intervention, Wilks` Lambda = .99, $F$ (2, 48) = .30, $p$ = .74. See Figure 5. There was no statistically significant interaction effect between number of previous depressive episodes and basal circadian cortisol variations after the 14-days intervention, Wilk`s Lambda = .95, F (2, 48) = 1.20, p = .32.

In the basal circadian cortisol curve after the 14-days intervention period, the evening sample in the placebo ABM group had a mean of 1.34 with a SE of 0.22, and in the active ABM group a mean of 0.99 and a SE of 0.18. The Morning 1 sample in the placebo ABM group had a mean of 4.64 with a SE of 0.49, and the active ABM group had a mean of 4.57

and a SE of 0.51. The Morning 2 sample in the placebo ABM group had a mean of 5.72 and a SE of 0.56, and in the active ABM group with a mean of 5.47 and a SE of 0.65. See Figure 5.

Figure 5. Basal circadian cortisol variations after the 14-days ABM intervention

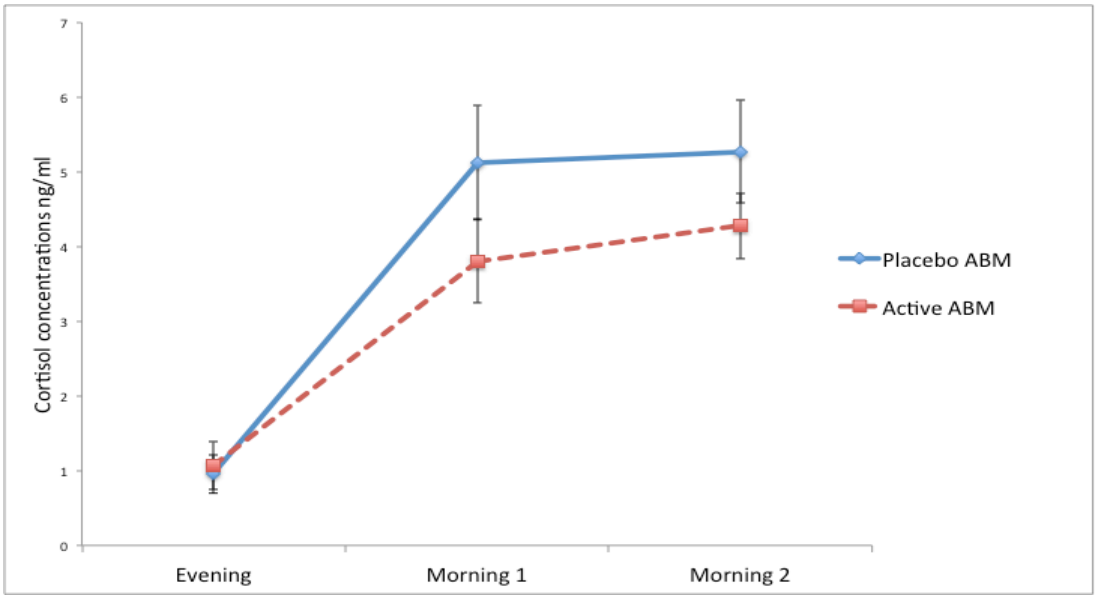


Note. Depicting basal circadian cortisol variations from evening to morning after the 14-days ABM intervention. Cortisol concentrations measured in ng/ml in the evening (Evening), upon wakening (Morning 1) and 15 minutes after the first morning sample (Morning 2). The filled line shows the placebo ABM group, and the dotted line shows the active ABM group.

The third hypothesis was that the difference in basal circadian cortisol variations between the two groups would be more apparent at the one-month follow up. There was no statistically significant interaction effect between the ABM conditions and basal circadian cortisol at the one-month follow up, Wilks` Lambda = .97, $F$ (2, 38) = .70, $p$ = .51. See Figure 6. There was also no statistically significant interaction effect between number of previous depressive episodes and basal circadian cortisol variations at one-month follow up, Wilks` Lambda = .97, F (2, 38) = .47, p = .63.

In the basal circadian cortisol curve at one-month follow up, the evening sample in the placebo ABM group had a mean of 0.96 with a SE of 0.26, and in the active ABM group a mean of 1.07 and a SE of 0.32. The Morning 1 sample in the placebo ABM group had a mean of 5.13 with a SE of 0.77, and the active ABM group had a mean of 3.81 and a SE of 0.56. The Morning 2 sample in the placebo ABM group had a mean of 5.27 and a SE of 0.69, and in the active ABM group with a mean of 4.28 and a SE of 0.44. See Figure 6.

Figure 6. Basal circadian cortisol variations at one-month follow up

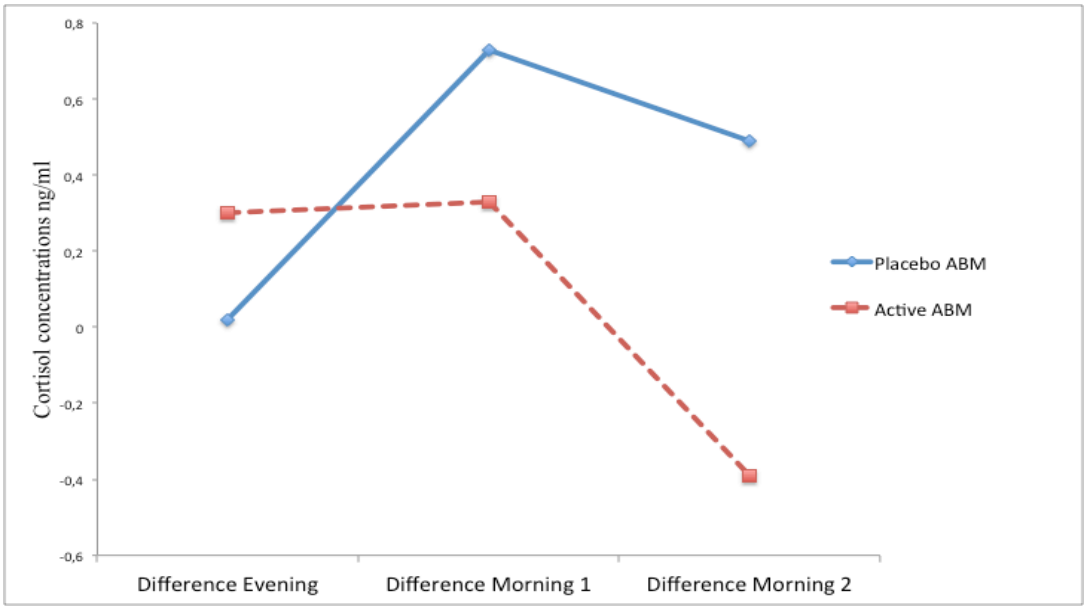


Note. Depicting basal circadian cortisol variations from evening to morning at one month-follow up after the ABM training. Cortisol concentrations measured in ng/ml in the evening (Evening), upon wakening (Morning 1) and 15 minutes after the first morning sample (Morning 2). The filled line shows the placebo ABM group, and the dotted line shows the active ABM group.

To look at possible changes between the different cortisol samples before the intervention, at 14-days follow up and at one-month follow up, difference scores were as previously mentioned calculated. There was no statistically significant interaction effect between the ABM conditions and difference scores in basal circadian cortisol from pre intervention to the 14-days follow up, Wilks` Lambda = .98, $F$ (2, 48) = .54, $p$ = .59. See Figure 7. There was no statistically significant interaction effect between number of previous depressive episodes and differences in basal cortisol variations between pre to the 14-days follow up, Wilks` Lambda = .95, F (2, 48) = 1.34, p = .27.

The difference score for the Evening sample in the placebo ABM group had a mean of -.02, and in the active ABM group a mean of .30. The difference score for the Morning 1 sample in the placebo group had a mean of .73, and in the active ABM group a mean of .33. The difference score for the Morning 2 sample had a mean of .49 in the placebo ABM group, and a mean of -.39 in the active ABM group. See Figure 7.

Figure 7. Mean difference between cortisol samples pre intervention and at 14-days follow up in the two groups

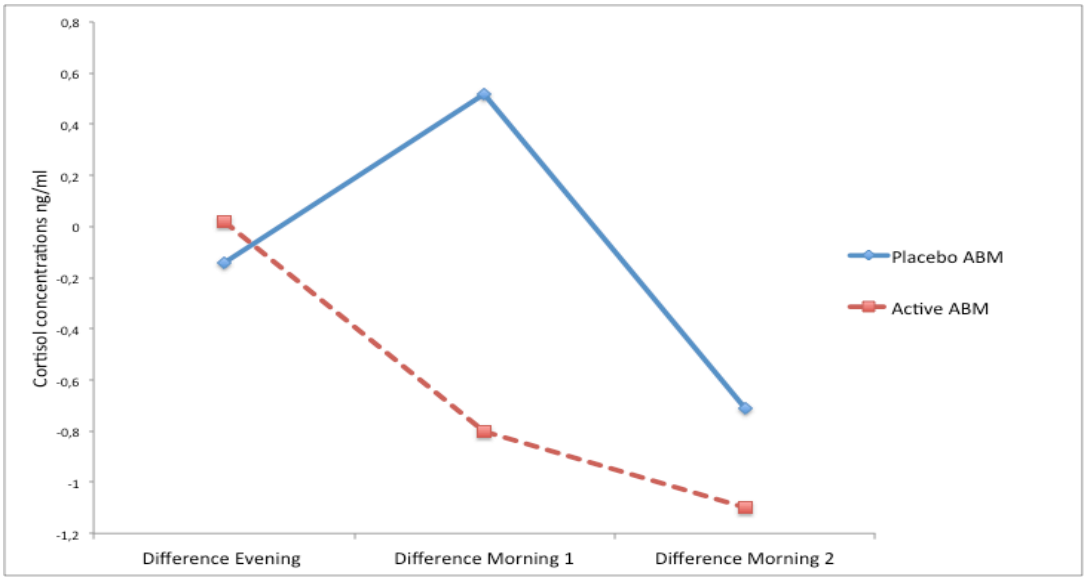


Note. Depicting the mean difference scores between the Evening, Morning 1 and Morning 2 samples from before and after the 14-days intervention. The filled line shows the placebo ABM group, and the dotted line shows the active ABM group.

There was no statistically significant interaction effect between the ABM conditions and difference scores in basal circadian cortisol from the 14-days follow up to the one-month follow up, Wilks` Lambda = .95, $F$ (2, 38) = 1.00, $p$ = .38. . See Figure 8. There was no statistically significant interaction effect between number of previous depressive episodes and differences in basal cortisol variations between the 14-days follow up to the one-month follow up, Wilks` Lambda = .98, F (2, 38) = .45, p = .64.

The difference score for the Evening sample in the placebo ABM group had a mean of -.14, and in the active ABM group a mean of .02. The difference score for the Morning 1 sample in the placebo group had a mean of .52, and in the active ABM group a mean of -.80. The difference score for the Morning 2 sample had a mean of -.71 in the placebo ABM group, and a mean of -1.10 in the active ABM group. See Figure 8.

Figure 8. Mean differences between cortisol samples at the 14-days follow up and one-month follow up in the two groups

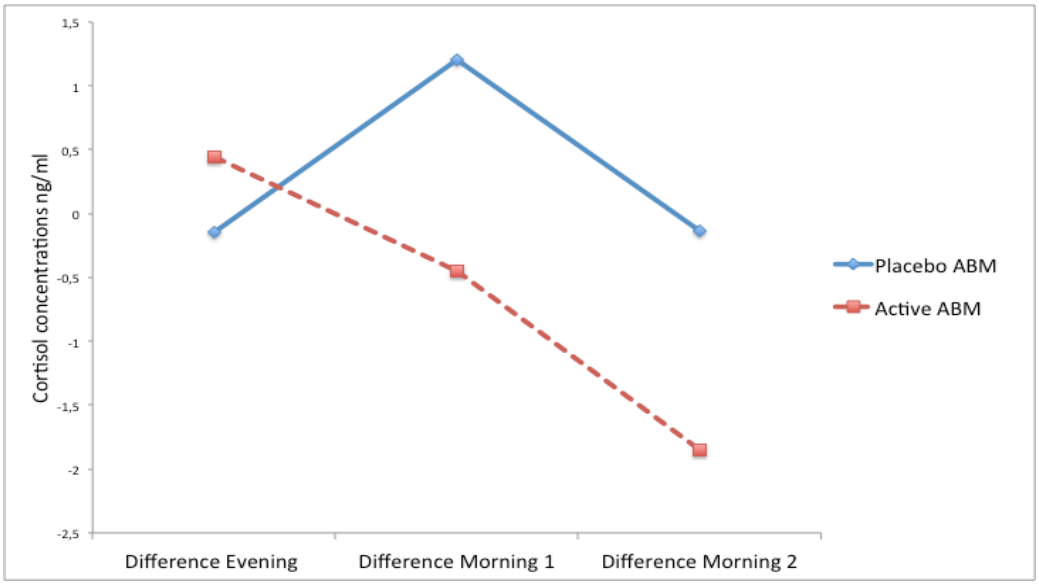


Note. Depicting the difference scores between the Evening, Morning 1 and Morning 2 samples from the 14-dats follow up and the one-month follow up. The filled line shows the placebo ABM group, and the dotted line shows the active ABM group.

There was no statistically significant interaction effect between the ABM conditions and difference scores in basal circadian cortisol from pre to the one-month follow up, Wilks` Lambda = .93, $F$ (2, 38) = 1.46, $p$ = .25. See Figure 9. There was no statistically significant interaction effect between number of previous depressive episodes and differences in basal circadian cortisol variations between from pre to the one-month follow up, Wilks` Lambda = .94, F (2, 38) = 1.12, p = .34.

The difference score for the Evening sample in the placebo ABM group had a mean of -.15, and in the active ABM group a mean of .44. The difference score for the Morning 1 sample in the placebo group had a mean of 1.21, and in the active ABM group a mean of -.45. The difference score for the Morning 2 sample had a mean of -.14 in the placebo ABM group, and a mean of -1.85 in the active ABM group. See Figure 9.

Figure 9. Mean difference between cortisol samples pre intervention and at one-month follow up in the two groups



Note. Depicting the difference scores between the Evening, Morning 1 and Morning 2 samples from the before the intervention and one-month follow up. The filled line shows the placebo ABM group, and the dotted line shows the active ABM group.

Table 3. Difference scores for basal circadian cortisol variations between the two groups at the different times of measurement

	Pre (T1) to 14-days follow up (T2)		**14-days follow up (T2) to one-month follow up (T3)**		**Pre (T1) to one-month follow up (T2)**	
	Placebo (*n* = 25)	**Active (*n* = 27)**	**Placebo (*n* = 18)**	**Active (*n* = 24)**	**Placebo (*n* = 18)**	**Active (*n* = 24)**
Evening Mean (SE)	*.02 (.19)*	*.30 (.17)*	*-.14 (.30)*	*.02 (.38)*	*-.15 (.39)*	*.44 (.36)*
Morning 1, Mean (SE)	*.73 (.53)*	*.33 (.44)*	*.52 (.88)*	*-.80 (.62)*	*1.21 (.79)*	*-.45 (.74)*
Morning 2, Mean (SE)	*.49 (.55)*	*-.39 (.68)*	*-.71 (.75)*	*-1.10 (.74)*	*-.14 (.76)*	*-1.85 (.88)*

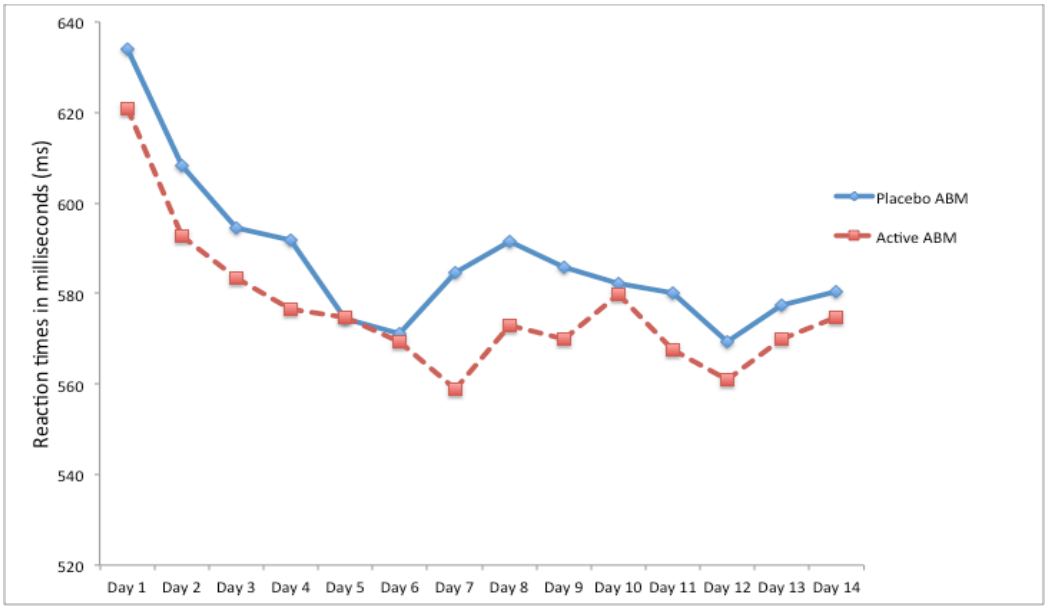
3.4 Secondary aims

3.4.1 The general learning effect of the ABM task

One of the secondary aims was that both groups would show a general learning effect over the 14-days intervention, towards both valid and invalid trials over the 14-days intervention with the ABM task.

There was a statistically significant main effect of time for valid trials, Wilks` Lambda = .33, F (13, 36) = 5.58, p = .00. See Figure 10.

Figure 10. Reaction times towards valid trials

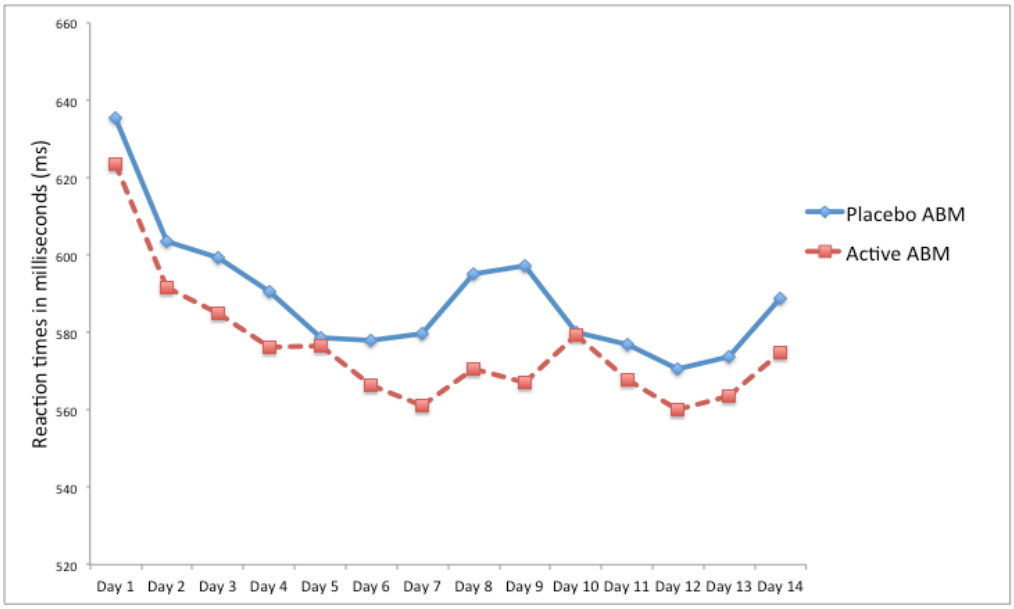


Note. The mean average of reaction times towards valid trials (i.e. positive valence faces) from each of the 14-days intervention for both of the groups.

There was also a statistically significant main effect of time for invalid trials, Wilks` Lambda = .30, F (13, 36) = 6.35, p = .00. See Figure 11.

In sum, there was a statistical significant difference between reaction times towards both valid and invalid trials from the beginning of the 14-days training period until the end of the training period regardless of condition, establishing the predicted general learning effect.

Figure 11. Reaction times towards invalid trials



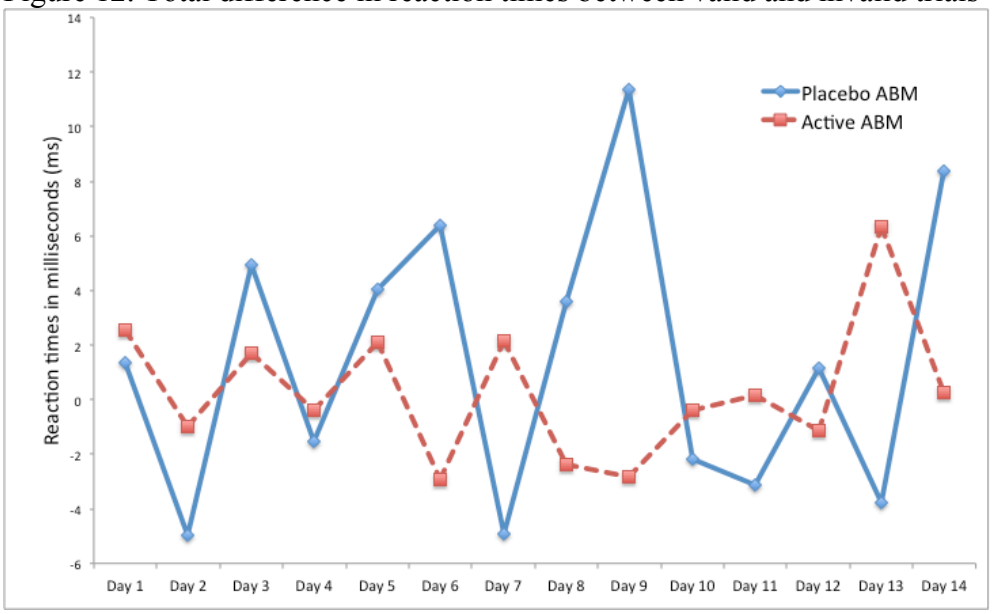
Note. The mean average of reaction times towards invalid trials (i.e. negative valence faces) from each of the 14-days intervention for both of the groups.

3.4.2 Fluctuations in biases

The other secondary aim was to investigate possible fluctuations, entailing a difference in reaction times between valid and invalid trials in the two groups. There was however no main effect of time, meaning no statistically significant difference in reaction times between valid and invalid trials regardless of condition, Wilks`Lambda = .72, $F$ (13, 36) = 1.10, $p$ = .42. There was also no statistically significant interaction effect between the ABM conditions and differences in reaction times between valid and invalid trials, Wilks` Lambda = .68, F (13, 36) = 1.33, p = .32. See Figure 12.

In sum there appeared to be fluctuations in both groups in differences in reactions times between valid and invalid trials, as depicted in Figure 12, but no statistically significant effects.

Figure 12. Total difference in reaction times between valid and invalid trials



The mean average of the difference in reaction times between valid and invalid trials from each of the 14-days intervention for both of the groups.

4 Discussion

4.1 Main findings

4.1.1 Basal circadian cortisol variations

The first hypothesis of the current study was to investigate if basal circadian cortisol levels would decrease in the evening and increase from the first to the second morning sample, in both of the groups at all three times of measurement. In accordance with this hypothesis, there was a consistent finding of the predicted basal circadian cortisol variations both before and after the ABM intervention and at one-month follow up. This was an important finding in order to validate the expected curve, before possible effects of the ABM task on these basal circadian cortisol variations could be evaluated.

4.1.2 The association between basal circadian cortisol variations and the ABM task

The second hypothesis of the study was to investigate if there was a difference in basal circadian cortisol variations between the two groups after the 14-days intervention. The third hypothesis was that this effect would be more apparent at one-month follow up than after the 14-days intervention. The findings were at odds with both of these hypotheses. There was no statistically significant difference between the two groups with regards to changes in basal circadian cortisol, at either of the two times of measurement after the intervention. This entailed both the basal circadian curves, and for the differences scores between the cortisol samples at the different times of measurement.

The estimated power of the results was small. Meaning that if there was an actual decrease of cortisol in the predicted direction, there would be a small probability of finding that effect in the current sample given its total number of participants. Looking at tendencies in the predicted direction in the data was therefore of interest.

4.1.3 Difference scores in basal circadian cortisol between the different times of measurement

The predicted direction of cortisol levels was a decrease in concentrations for all three samples. When calculating difference scores between the different times of measurement, positive scores would indicate an increase in cortisol concentrations and negative scores would indicate a decrease in cortisol concentrations. If there was any tendencies in the predicted direction with regards to differences scores, the expect results would be a decrease in cortisol in the difference scores for both the Evening, Morning 1, and Morning 2 samples,

between 14-days follow up and pre intervention, and an even greater decrease in the difference scores between one-month follow up and pre intervention, and a moderate decrease between one-month and 14-days follow up. See Table 3.

In sum, there appeared to be a tendency of a decrease in cortisol concentrations in the active ABM group for the Morning 2 samples from pre to 14-days follow up, from 14-days follow up to one-month follow up, and from pre to one-month follow up. This was a non-statistically significant decrease in cortisol concentrations in the predicted direction. As predicted, the greatest difference was between pre and one-month follow up samples, and a slightly smaller decrease between 14-days follow up and one-month. There was also some decrease between the different times of measurement in the placebo ABM group, but these were slightly smaller that in the active group, and less consistent.

It appeared however that the decrease in cortisol in the predicted direction only was a consistent tendency for the Morning 2 samples in the active ABM group. The cortisol awakening response has been the most prominent marker of a heightened basal cortisol level in previously depressed individuals. Studies have found a blunted basal circadian cortisol curve, which also entails evening samples. Investigating these basal variations over a 24 hours period can be an important contribution in order to increase knowledge of possible fluctuations in basal cortisol in relation to depression. However, differences in cortisol concentrations in the evening might need to be established through several cortisol samples taken over one or several consecutive hours, in order to reveal possible elevations and reductions in cortisol levels.

The standard errors of the above-discussed findings were high. There can be great inter-individual variance in cortisol levels, which may partly explain this. In addition, the difference between two cortisol samples can entail a high degree of variation, both between subjects and between different times of measurements for an individual. Thus interpretation of the tendencies must be done with caution due to the high standard errors. However, one can speculate that these tendencies might have been statistically significant in a bigger sample.

4.1.4 The ABM learning effect

As one of the secondary aims, the study investigated if both of the groups would show a learning effect from the ABM task during the 14-days intervention, defined as a statistically significant decrease in reaction time. There was a general learning effect of the ABM task in both of the groups, expressed as a statistically significant decrease in reaction times towards

both valid and invalid trials in both of the groups. Establishing this general learning effect validates the fact that the participants completed their sessions during the 14-days intervention in a satisfactory way. This should be established before one can evaluate possible effects of the ABM task.

There was a statistically significant decrease in reaction times in both of the groups between the first days of the ABM task. This learning effect gradually flattened around day 4-6, and then there were some fluctuations in reaction times over the remaining days. It appeared that the attention bias training did not have a specific effect on positive vigilance.

4.2 Additional findings and considerations

4.2.1 The ABM task – fluctuations in attention biases

Since the current study was able to establish a general learning effect of the ABM task in both of the groups, the non-statistically significant findings in the current study was not due to lack of having completed the intervention.

Another secondary aim was to investigate possible fluctuations in biases. There were no statistically significant effects, but there were however some tendencies in the direction of more noticeable fluctuations in the placebo ABM group compared to the active ABM group.

Figure 12. shows differences in reaction times between valid and invalid trails in the two groups. This curve shows that at the first day, the placebo group in general shows a faster reaction time towards negative stimuli than towards positive stimuli. While the active ABM group in general shows a faster reaction time towards positive stimuli. When looking at the differences in reaction times between the two groups on the first day, it gives the impression of a pre-existing positive bias in the active ABM group and a negative bias in the placebo group. However, when looking at these biases from day to day, they appear to be continuously shifting between negative and positive. Measuring a pre-existing bias can therefore be difficult. Using baseline measures where reaction times towards positive and negative valence faces before and after an intervention through a dot-probe paradigm is compared, can be a poor measure of the effects of the ABM intervention.
Such baseline measures before and after CBM interventions have been frequently used. Apparent statistically significant effects might then be due to other unexplained factors (i.e. error variance) when measuring biases as stable traits before and after the interventions.

If attention biases are viewed as more dynamic processes (Zvielli et al., 2015) these biases would be expected to fluctuate, but the degree of fluctuations, might be affected by the ABM task. As depicted in Figure 12., the fluctuations within the active ABM group appear to

be smaller than in the placebo ABM group. This might indicate that the ABM task can affect the degree of fluctuations, which could have explained the tendency of a reduction in basal cortisol in the predicted direction in the active group. The ABM task aims to modify a negative attention bias. This bias might however be a more dynamic process that fluctuates in accordance with mood, and a reduction in fluctuations might indicate a less easily evoked negative attention bias, that is less influenced by negative mood.

Establishing pre-existing biases can be challenging, due to great fluctuations as shown in Figure 12., and also pointed out in the study by Zvielli et al. (2015). Trying to establish the dynamics of attention biases preceding ABM interventions, could give a better indication of possible effects. The current study showed some of these fluctuations, and a possible stabilization of these, but did not investigate what affected them. This could be connected to a number of factors like current symptom level, number of previous depressive episodes, genes and comorbid psychiatric diagnoses. The current study included factors with regards to symptom level, age, education and gender. However, these were measured in order to look for possible group differences, and not to look at possible mediating effects they could have on the association between the ABM task and basal cortisol.

In their review on the current standing on cognitive bias modification research and recommendations for future research, Koster and Bernstein (2015) emphasize that studies with null findings make important contributions when it comes to the future development and adjustments to cognitive bias modifications methods. The findings from the currents study are therefore interesting to further our understanding of possible adjustments needed to the ABM task. Especially with regards to pre-existing and fluctuating biases, which might contribute the field to "take a step back to move forward"(Koster & Bernstein, 2015).

4.2.2 Factors influencing degree of malleability in depressive schemas

An attention bias can as mentioned be viewed as being at the centre of depressive schemas. These schemas become more easily activated with each depressive episode, and more resistant to change during an episode. In the current study, there were differences between the two groups that could have had an impact on degree of malleability in the depressive schemas, and therefore modification of an attention bias. In addition, the sample in the current study might have been a more heterogeneous sample of previously depressed compared to previous studies within the field.

There was a higher mean average of previous depressive episodes in the active ABM group compared to the placebo ABM group. Given the fact that 30% relapses within 3

months of their depressive episode (Browning et al., 2012), one can assume that a portion of the participants would enter a new depressive episodes within the one-month period. As mentioned, the risk for relapse increases with the number of previous episodes, like a kindling effect. This would be especially relevant for the active ABM group, given their higher mean average of previous episodes. Another fact that supports this assumption is that the mean average of BDI-II scores in the active ABM group was just within the cut-off criteria for remission. This cut-off criteria for remission might have been too liberal. Leading to a high sensitivity entailing correctly identifying those who were in remission, but maybe a reduced specificity in correctly identifying those who were not in current remission, but rather entering a new depressive episode.

In sum, there were a higher number of previous depressive episodes and BDI-II scores in the active ABM group. An attention bias would then be difficult to alter, when taken into consideration the assumption that the more activated the depressive schemas are, the more resistant to change they become. Also, number of previous depressive episodes, have been indicated to influence the degree of cognitive flexibility also in remission phases (Biringer et al., 2005). In people with a reduced degree of cognitive flexibility, it might be more difficult to affect their cognitive biases through associative learning.

The sample in the current study might better have reflected the heterogeneous group of previously depressed, compared to previous, similar studies that have had stricter remission criteria's. Some studies have had a time criteria for remission of six months (Browning et al., 2012), while the current study had a time criteria for remission of only two weeks. Studies have shown that individuals with a reduced responsiveness of the HPA axis in remission, are at higher risk for relapse (Zobel et al., 2001). Having been in remission for an extended amount of time might therefore indicate a better functioning HPA axis, more susceptible to experimental changes. Depressive schemas would then be less resistant to change, which would entail both the attention bias component and cortisol component of the schemas. Given the inter-related areas involved in both a negative attention bias and stress responses like the amygdala, it is likely that these processes will both reinforce and maintain each other.

The participants in the current study might have had more easily activated depressive schemas and subsequent rigidity in attention biases and HPA functioning that could have affected the null-findings. This is an important consideration when taking a step back to evaluate how ABM paradigms best can target vulnerabilities for maintenance and reoccurrence in the heterogeneous population of previously depressed.

However, the possible more heterogeneous sample in the current study, and the differences between the two groups, might have posed a challenge in obtaining statistically significant results in the predicted direction.

4.2.3 Comorbidity in depression and anxiety disorders

In the current study, many of the participants had a comorbid anxiety disorder, which could have influenced the lack of the predicted outcome effects from the ABM task on basal circadian cortisol.

The content specific hypotheses predicts that people suffering from depression or anxiety disorders, will show a content specific attention bias. These different, content specific attention biases in depression and anxiety, might occur at different stages of attention processes (Browning et al., 2010; Gotlib et al., 2004). The current study used an ABM task were faces were presented for either 1000ms or 500ms. Given the high comorbidity in the sample, the phenomenon of a content specific bias in depression, might not have been present in all of the participants in the sample. In addition, using both presentation times of 500ms and 1000ms, might not have targeted specifically enough the later stages of attention processes where the bias in depression might be most evident.

The sample in the current study might have given a more correctly reflection of the heterogeneous population of individuals in remission from depression, with regards to comorbidity. However, this complexity in the sample might have affected the results.

4.3 Sample size and estimated power

The different factors discussed so far, are important considerations in understanding the null-findings. However, the factors used in the analyses, both the ABM task and basal cortisol also depend on power. Estimated power of the findings revealed that if there had been a statistically significant difference in the population, there would be a low probability of finding the difference in the current sample, given its size. A high number of participants in a sample can make it sensitive to small, but sometimes insignificant effects. This can increase the probability for statistically significant findings that can also result in an overestimation of the effects of an intervention, a type 1 error. Whereas a small sample size can be more vulnerable of not detecting small effects that might be of significance, which decrease the probability of statistically significant findings, resulting in a possible under estimation of effects, a type 2 error (Field, 2013).

Even though the discussed reasons for possible null findings are important considerations, it is also important to view them in light of the low estimated power, which can be influence by a number of factors, but that also in itself could have led to an under estimation of possible effects of the ABM task on basal circadian cortisol variations.

4.4 Strength and limitations

4.4.1 Participants

The participants in the current study were recruited from an outpatient clinic. The sample might therefore be said to be representative of the population of previously depressed. This gives a good ecological validity, meaning that the sample reflects the actual target group with respects to variations in age, gender, and educational level, in addition to clinical status. Indicating a translation of possible effects to real-world settings (Field, 2013). The heterogeneity in the sample did also pose some challenges, due to the within-subjects variations with regards to several factors. However, studying a heterogeneous sample like this when assessing the association between the ABM task and residual symptoms (e.g. basal cortisol) is viewed as a strength in terms of possible translation to clinical applications of the task.

4.4.2 Number of training sessions in the current ABM task

The ABM task used in the current study had a relatively high number of sessions, 28, during the 14-days intervention, compared to other studies using similar procedures. Extending number of session but also the time range for the administration of sessions, gives an increased probability of cognitive changes that can be longer lasting (MacLeod et al., 2009). The time frame for the administration of the ABM task and number of sessions was therefore considered a strength in the current study.

4.4.3 Assessment of current symptom level and residual symptoms

Establishing reliable and valid assessments of current level of depressive symptoms is important when investigating the possible effects of an intervention like the ABM task on residual symptoms. When investigating the effect of the ABM task on residual symptoms, a combination of well validated self-report measures and physiological measures have been recommended in the literature(MacLeod et al., 2009). The current study used cortisol as an outcome measure, which would reflect possible physiological changes in depressive schemas as an effect of an attention modification, and the BDI-II as a self-report measure of current

level of depressive symptoms. Using a combination of a well-established valid self-report measure like the BDI-II and a physiological measurement like cortisol, are considered as strengths in the current study with regards to measurement.

4.4.4 Factors influencing basal circadian cortisol concentrations

The current study used three cortisol samples to establish basal circadian cortisol variations, as previously mentioned. Saliva cortisol samples can be unreliable when looking at samples separately, without creating a baseline consisting of several samples taking during one consecutive hour or hours. Factor influencing the samples leading to a possibly higher error variance can be circadian rhythms, gender, age (Kirschbaum & Hellhammer, 1994) or stressful events of the current morning or evening of the sampling time and antidepressants.

In some studies investigating the reliability of saliva cortisol samples, it has been noted that taking morning cortisol samples during the 30-60 first minutes after awakening with 15 minutes intervals, reduced the effects of factors which normally can have an effect on baseline levels (Pruessner et al., 1997). Using only one sample from the evenings, and two in the mornings with a 15-minute interval, might not have been sufficient to establish a stable measurement of basal circadian variations. The following factors were considered especially influential on basal cortisol in the current study; seasonal changes in cortisol, cortisol sampling time, age and antidepressants.

Seasonal changes consisting of longer or shorter periods with natural light during the daytime affect cortisol levels (Wehr, 1998). Even though artificial light in our modern society has made these seasonal changes less, it can still affect cortisol variations. The current study used cortisol data collected over one consecutive year, which means that the comparison of cortisol samples between the two groups, consisted of cortisol from all through the different season of the year with possibly subsequent variations.

Cortisol levels are also affected by circadian rhythms (Van Cauter et al., 1996). Variations in sleeping patterns, bedtime hours and time of wakening will therefor affect basal cortisol levels. The participants in the current study were instructed to take the saliva samples within a given time frame. However, many of the participants were not able to abide by these sampling times due to different circumstances ranging from simply forgetting to do the sample, to variations in circadian rhythms resulting in getting up after 09 for example. The cortisol data was not divided into time of sampling. The participants could have been divided into different groups according to sample time and circadian rhythms when analyzing basal circadian cortisol variations.

Since there was no statistically significant difference between the two groups with regards to age, it was not assessed as being a necessary covariate in the analyses. However, when using only three cortisol samples, the influence of factors like age, can lead to a less robust and reliable measure of basal cortisol, as previously mentioned. Age has been shown to impact variations in cortisol greatly (Van Cauter et al., 1996). The current sample consisted of participants with a range in age between 27-67. Not controlling for possible differences in cortisol variations due to age when only using three samples, could have been a limitation in establishing a reliable measure of basal cortisol, and revealing possible effects between the ABM task and basal cortisol.

The current study did not control for whether or not the participants were medicated with antidepressants. Different forms of antidepressants affect the HPA axis function, by increasing the number of GR receptors (Pariante et al., 2004), which often has been down regulated, or destroyed due to excessive cortisol release. When antidepressants are effective and work in the intended way, there can be an increase in both GR and MR that leads to a more functional negative feedback system in the HPA axis. Resulting in a better functioning stress response system, able to regulate itself when faced with stressors. If several of the participants were medicated with antidepressants during the intervention and at one-month follow up, this could have affected cortisol levels in the direction of more normal levels that would not be affected by possible effects by the ABM task.

There were also some constraints in the biological analysis of some of the cortisol samples, especially for the one-month follow up samples, which was the main reason there were only full cortisol sample sets for 42 of the 52 participants at one-month follow up.

In sum, both seasonal changes, variations in time of sampling, age, and the possible use of antidepressants, could have contributed to an unreliable measure of basal circadian cortisol. Not adjusting for these factors as covariates could therefore have been a limitation that might have contributed to masking possible effects of the ABM task.

4.5 A note on covariates

Since the use of antidepressant and age has both been shown to strongly influence cortisol concentrations, not adjusting for them as covariates could have been a clear limitation. The aim of including covariates is to reduce error variance (i.e. variance not explained by the independent variable). Some of the unexplained variance can then be explained by the covariates that can affect the dependent variable, which can lead to an increase in power estimations (Field, 2013). However, using several covariates can also lead to a reduction in

power, and must therefor be used with caution. In addition, within the scope of the current study it was not possible to investigate all of the possible confounding variables with regards to the association between the ABM task and cortisol. Finding alternative ways to deal with confounding variables might entail dividing the sample in different group when assessing the impact on these different factors on the associated relationship between attention modification and cortisol.

4.6 Suggestions for future research

Regardless of the possible mentioned limitations, the null-findings in the current study is considered to be a small but important contribution in the field of ABM targeted interventions for vulnerability of reoccurrence in depression. In the future, ABM procedures could represent a viable alternative to secondary prevention of reoccurrence in depression. In order to evaluate whether or not this method could be effective and translated into a clinical setting, studies aiming to better understand and optimizing the method are important.

One recommendation would be to investigate the possible effects of third variables. This could be important in order to get a better understanding of factors that could mediate the effect of the ABM on residual symptoms in depression. Third variables that would be interesting to investigate more closely are number of previously depressive episodes and comorbid anxiety disorder. Given the high comorbidity between anxiety disorders and depression, these affective disorders share some features, but are more distinct with regards to others, which include differences in attention biases. Investigating samples of previously depressed with no comorbid anxiety disorders and using stimuli durations for 1000ms, could be one option. Another option is to investigate possible combinations of duration of stimuli presentation and stimuli content. In order to assess what form of the ABM task that would be most efficiently in such a heterogeneous population.

Number of previous depressive episodes could as mentioned have an effect on degree of malleability in depressive schemas, which should be investigated more closely.

Looking at pre-existing attention biases as dynamic processes could yield interesting results, in the further development of the ABM task.

Establishing a robust measure of basal cortisol with an increased number of cortisol samples that could reduce degree of possible error variance could be an important step. Looking at circadian variations through basal circadian cortisol variations however, and not only the cortisol awakening response, is recommended in order to increase the understanding of basal cortisol as a residual symptoms in depression. The CAR has been widely

investigated, and has been established as being increased both during depressive episodes and remission periods. In order to get a more comprehensive understanding of basal cortisol in relation to attention in depression, circadian variations will possibly to a greater degree reflect the overall functioning of the HPA axis.

4.7 Clinical implications

Finding novel ways to prevent reoccurrence in depression is an important step in reducing the burden of the disorder. As shown in the study by Schmidt et al. (2009), ABM procedures can markedly reduce symptoms in affective disorders, especially anxiety disorders. This indicates a possible translational value of the ABM procedure to clinical settings, and it might be possible in the future to produce similar effects in samples of previously depressed individuals in remission.

The finding in the current study has made some contributions with regards to possible needed adjustments and considerations when using the ABM task.

The ABM procedure can in the future prove to be an effective alternative in the prevention of reoccurring depressive episodes; it can be used by people in their own homes administrated in a computerized form, which can be maintained over time. This might prove to be a cost-effective intervention in treating reoccurrence in depression.

4.8 Conclusion

The aim of the current study was to investigate the association between attention bias modification and basal circadian cortisol in individuals vulnerable for reoccurrence in depression. Both of the groups showed the expected basal circadian variations, with a decrease in cortisol concentrations in the evening, and an increase from the first to the second morning sample. The association between the ABM task and basal circadian cortisol was however not statistically significant. There were however tendencies in the predicted direction of a reduction in basal cortisol in the active ABM group, mainly for the morning cortisol samples.

Both of the groups showed a learning effect towards both valid and invalid trials. There also appeared to be a fluctuation in attention biases when comparing the differences in reaction times between valid and invalid trials. These fluctuations were greater in the placebo ABM group compared to the active ABM group. The reduction in fluctuation in biases, might explain the tendencies of a reduction in basal cortisol on the active ABM group.

A number of factors could have influenced the current null-findings: current symptom level, number of previous depressive episodes, criteria for length of time in remission, comorbid anxiety disorders and establishing reliable basal circadian cortisol measures. In addition, the estimated power in the current sample was low, which could have made under estimations of possible effects likely.

The null-findings in the current study is considered to be a small but important contribution to the field of attention bias modification and depression, in terms of re-evaluating different aspects of the intervention with regards to fluctuations in biases, duration and content of stimuli, possible confounding third variables, and establishing reliable outcome measures.

References

Andreotti, C., Garrard, P., Venkatraman, S. L., & Compas, B. E. (2014). Stress-Related Changes in Attentional Bias to Social Threat in Young Adults: Psychobiological Associations with the Early Family Environment. *Cognitive Therapy and Research, 39*(3), 332-342.

Beck, A. T. (1967). *Depression : clinical, experimental, and theoretical aspects*. New York: Hoeber Medical Division.

Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *American Journal of Psychiatry, 165*(8), 969-977. doi:10.1176/appi.ajp.2008.08050721

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical psychology review, 8*(1), 77-100.

Biringer, E., Lundervold, A., Stordal, K., Mykletun, A., Egeland, J., Bottlender, R., & Lund, A. (2005). Executive function improvement upon remission of recurrent unipolar depression. *European Archives of Psychiatry and Clinical Neuroscience, 255*(6), 373-380.

Browning, M., Holmes, E. A., Charles, M., Cowen, P. J., & Harmer, C. J. (2012). Using attentional bias modification as a cognitive vaccine against depression. *Biological psychiatry, 72*(7), 572-579.

Browning, M., Holmes, E. A., & Harmer, C. J. (2010). The modification of attentional bias to emotional information: A review of the techniques, mechanisms, and relevance to emotional disorders. *Cognitive, Affective, & Behavioral Neuroscience, 10*(1), 8-20.

Colman, A. M. (2008). ICD-10 (3 ed. ed.): Oxford University Press.

Cuijpers, P., Smit, F., Bohlmeijer, E., Hollon, S. D., & Andersson, G. (2010). Efficacy of cognitive–behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. *The British Journal of Psychiatry, 196*(3), 173-178.

de Kloet, E. R., Oitzl, M. S., & Joëls, M. (1999). Stress and cognition: are corticosteroids good or bad guys? *Trends in neurosciences, 22*(10), 422-426.

De Raedt, R., & Koster, E. H. W. (2010). Understanding vulnerability for depression from a cognitive neuroscience perspective: A reappraisal of attentional factors and a new

conceptual framework. *Cognitive, Affective, & Behavioral Neuroscience, 10*(1), 50-70.

Deprimere. (n.d.). Oxford Dictionaries Online. Retrieved from http://www.oxforddictionaries.com/definition/english/depression

Disner, S. G., Beevers, C. G., Haigh, E. A., & Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience, 12*(8), 467-477.

Dozois, D. J., Dobson, K. S., & Ahnberg, J. L. (1998). A psychometric evaluation of the Beck Depression Inventory–II. *Psychological assessment, 10*(2), 83-89.

Fanselow, M. S., & Poulos, A. M. (2005). The neuroscience of mammalian associative learning. *Annual Review of Psychology, 56*, 207-234.

Field, A. (2013). *Discovering statistics using IBM SPSS statistics*. London: Sage.

Fox, E., Mackintosh, B., & Holmes, E. A. (2014). Travellers' tales in cognitive bias modification research: A commentary on the special issue. *Cognitive Therapy and Research, 38*(2), 239-247.

Gorissen, M., Bernier, N. J., Manuel, R., de Gelder, S., Metz, J. R., Huising, M. O., & Flik, G. (2012). Recombinant human leptin attenuates stress axis activity in common carp (Cyprinus carpio L.). *General and comparative endocrinology, 178*(1), 75-81.

Gotlib, I. H., Krasnoperova, E., Yue, D. N., & Joormann, J. (2004). Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of abnormal psychology, 113*(1), 127.

Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology, 58*, 145-173.

Hammen, C., Marks, T., DeMayo, R., & Mayol, A. (1985). Self-schemas and risk for depression: a prospective study. *Journal of Personality and Social Psychology, 49*(5), 1147-1159.

Harkness, K. L., Stewart, J. G., & Wynne-Edwards, K. E. (2011). Cortisol reactivity to social stress in adolescents: role of depression severity and child maltreatment. *Psychoneuroendocrinology, 36*(2), 173-181.

Holsboer, F. (2001). Stress, hypercortisolism and corticosteroid receptors in depression: implicatons for therapy. *Journal of affective disorders, 62*(1), 77-91.

Huber, T. J., Issa, K., Schik, G., & Wolf, O. T. (2006). The cortisol awakening response is blunted in psychotherapy inpatients suffering from depression. *Psychoneuroendocrinology, 31*(7), 900-904.

Kaufman, J., & Charney, D. (2000). Comorbidity of mood and anxiety disorders. *Depression and anxiety, 12*(1), 69-76.

Kirsch, I., Deacon, B. J., Huedo-Medina, T. B., Scoboria, A., Moore, T. J., & Johnson, B. T. (2008). Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med, 5*(2), e45.

Kirschbaum, C., & Hellhammer, D. H. (1994). Salivary cortisol in psychoneuroendocrine research: recent developments and applications. *Psychoneuroendocrinology, 19*(4), 313-333.

Koster, E. H. W., & Bernstein, A. (2015). Introduction to the special issue on Cognitive bias modification: Taking a step back to move forward? *Journal of Behavior Therapy and Experimental Psychiatry, 49*(Pt A), 1-4. doi:10.1016/j.jbtep.2015.05.006

Koster, E. H. W., Fox, E., & MacLeod, C. (2009). Introduction to the special section on cognitive bias modification in emotional disorders. *Journal of abnormal psychology, 118*(1), 1.

Lacey, J. I. (1956). The evaluation of autonomic responses: Toward a general solution. *Annals of the New York Academy of Sciences, 67*(5), 125-163.

Liu, R. T., & Alloy, L. B. (2010). Stress generation in depression: A systematic review of the empirical literature and recommendations for future study. *Clinical psychology review, 30*(5), 582-593.

MacLeod, C., Koster, E. H. W., & Fox, E. (2009). Whither cognitive bias modification research? Commentary on the special section articles. *Journal of abnormal psychology, 118*(1), 89-99.

Marcus, M., Yasamy, M. T., Van Ommeren, M., Chisholm, D., & Saxena, S. (2012). Depression: A global public health concern. Retrieved from http://www.who.int/mental_health/management/depression/who_paper_depression_wfmh_2012.pdf?ua=1

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology, 1*, 167-195.

McEwen, B. S. (1998). Protective and Damaging Effects of Stress Mediators. *New England journal of medicine, 338*(3), 171-179.

Meiran, N., Diamond, G. M., Toder, D., & Nemets, B. (2011). Cognitive rigidity in unipolar depression and obsessive compulsive disorder: Examination of task switching, Stroop, working memory updating and post-conflict adaptation. *Psychiatry Research, 185*(1), 149-156.

Mordal, J., Gundersen, Ø., & Bramness, J. (2010). Norwegian version of the Mini-International Neuropsychiatric Interview: feasibility, acceptability and test-retest reliability in an acute psychiatric ward. *European Psychiatry, 25*(3), 172-177.

Pariante, C. M., Thomas, S. A., Lovestone, S., Makoff, A., & Kerwin, R. W. (2004). Do antidepressants regulate how cortisol affects the brain? *Psychoneuroendocrinology, 29*(4), 423-447.

Preiss, M., Kucerova, H., Lukavsky, J., Stepankova, H., Sos, P., & Kawaciukova, R. (2009). Cognitive deficits in the euthymic phase of unipolar depression. *Psychiatry Research, 169*(3), 235-239.

Pruessner, J., Wolf, O., Hellhammer, D., Buske-Kirschbaum, A., Von Auer, K., Jobst, S., . . . Kirschbaum, C. (1997). Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life sciences, 61*(26), 2539-2549.

Riedel, M., Möller, H.-J., Obermeier, M., Schennach-Wolff, R., Bauer, M., Adli, M., . . . Laux, G. (2010). Response and remission criteria in major depression–a validation of current practice. *Journal of psychiatric research, 44*(15), 1063-1068.

Schatz, C. J. (1992). The developing brain. *Scientific American, 267*(3), 60-67.

Schmidt, N. B., Richey, J. A., Buckner, J. D., & Timpano, K. R. (2009). Attention training for generalized social anxiety disorder. *Journal of abnormal psychology, 118*(1), 5.

Sjögren, E., Leanderson, P., & Kristenson, M. (2006). Diurnal saliva cortisol levels and relations to psychosocial factors in a population sample of middle-aged Swedish men and women. *International Journal of Behavioral Medicine, 13*(3), 193-200.

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *Journal of psychosomatic research, 53*(4), 865-871.

Unesco. (1997). *International Standard Classification of Education-ISCED 1997: November 1997*: Unesco.

Van Cauter, E., Leproult, R., & Kupfer, D. J. (1996). Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *The Journal of Clinical Endocrinology & Metabolism, 81*(7), 2468-2473.

Wehr, T. A. (1998). Effect of seasonal changes in daylength on human neuroendocrine function. *Hormone Research in Paediatrics, 49*(3-4), 118-124.

World Health, O. (1993). *The ICD-10 classification of mental and behavioural disorders : diagnostic criteria for research*. Geneva: World Health Organization.

Zobel, A. W., Nickel, T., Sonntag, A., Uhr, M., Holsboer, F., & Ising, M. (2001). Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression: a prospective study. *Journal of psychiatric research, 35*(2), 83-94.

Zvielli, A., Amir, I., Goldstein, P., & Bernstein, A. (2015). Targeting Biased Emotional Attention to Threat as a Dynamic Process in Time: Attention Feedback Awareness and Control Training (A-FACT). *Clinical Psychological Science*. doi:10.1177/2167702615588048